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Research Article

Drug Use Evaluation on Type 2 Diabetes Mellitus and Diabetic Nephropathy Inpatients in One of Hospitals in Tasikmalaya

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Abstract
Type 2 diabetes mellitus (T2DM) is a degenerative disease and approximately 50% of patients with diabetes mellitus (DM) of more than 20 years' duration also have diabetic nephropathy (DN). T2DM accounts for significant morbidity and mortality, however appropriate treatment can reduce the events. The objective of the study was to evaluate of drug use in inpatient T2DM and DN. This was a cross-sectional study with concurrent data retrieval on T2DM and DN inpatients in the period of March–June 2017 in one of hospitals in Taskimalaya, Indonesia. Forty-six patients were included in the study, of which 25 patients had T2DM and 21 had DN. The result of this study showed that appropriateness of drug selection reached 100% and 85.6% in T2DM and DN inpatients, respectively. Inappropriateness of drugs selection includes selection of ketorolac, ranitidine, folic acid, amlodipine and potassium containing drugs. Doses accuracy of T2DM patients reached 100% and of DN inpatients reached 92.1%. The inaccuracy of doses was due to the lack of dose adjustment to estimated glomerulus filtration rate (eGFR) level in each patient. Drugs interaction analysis showed a potential drug interaction on DN and T2DM which devided into major (13.8%; 7.2%), moderate (64.1%; 58%) and minor (22,1%; 34.8%). Based on the result, it is found an inappropriate drug selection and an inaccuracy of dose in DN patients, and a high percentage of drugs interaction on moderate classification in both diseases. It is necessary to optimize the role of pharmacist as a part of the healthcare team in the patient's room to apply medication therapy management.

Keywords: Diabetic nephropathy, drug use evaluation, type 2 diabetes mellitus

Evaluasi Penggunaan Obat pada Pasien Rawat Inap Diabetes Melitus Tipe 2 dan Nefropati Diabetik di Salah Satu Rumah Sakit di Tasikmalaya

Abstrak
Diabetes melitus tipe 2 (DMT2) merupakan penyakit degeneratif dan sekitar 50% dari pasien yang telah menderita penyakit diabetes melitus (DM) selama lebih dari 20 tahun juga menderita penyakit nefropati diabetik (ND). Penyakit DMT2 dan nefropati diabetik mengakibatkan tingginya angka morbiditas dan mortalitas. Akan tetapi, penatalaksanaan terapi yang tepat dapat menurunkan kejadian tersebut. Tujuan penelitian ini adalah untuk melakukan evaluasi penggunaan obat pada pasien rawat inap dengan penyakit DMT2 dan ND. Penelitian ini menggunakan metode *cross-sectional* dengan pengambilan data secara konkuren terhadap pasien rawat inap DMT2 dan ND pada periode Maret–Juni tahun 2017 di salah satu rumah sakit di Tasikmalaya, Indonesia. Empat puluh enam pasien diikutsertakan, dengan 25 pasien menderita penyakit DMT2 dan 21 pasien menderita ND. Dari hasil penelitian ini, diperoleh ketepatan penggunaan obat pada penderita DMT2 mencapai 100% sedangkan pada penderita ND mencapai 85,6%. Ketidaktepatan pemilihan obat meliputi pemilihan ketorolac, ranitidine, asam folat, amlodipine dan kalium klorida. Ketepatan dosis pada penderita DMT2 mencapai 100%, sedangkan pada penderita ND mencapai 92,1%. Ketidaktepatan dosis disebabkan oleh tidak adanya penyesuaian dosis dengan nilai *estimated glomerulus filtration rate* (eGFR) terhadap pasien. Selain itu, ditemukan potensi interaksi obat pada penderita ND dan DMT2 yang diklasifikasikan ke dalam kategori mayor (13,8%; 7,2%), moderat (64,1%; 58%), dan minor (22,1%; 34,8%), secara berturut-turut. Berdasarkan hasil penelitian, ditemukan ketidaktepatan pemilihan obat dan ketidaktepatan dosis pada pasien ND serta tingginya persentase potensi interaksi obat, terutama kategori moderat, pada kedua penyakit. Diperlukan optimalisasi peran apoteker sebagai bagian dari tim di ruangan pasien rawat inap untuk melakukan penerapan pemantauan terapi obat.

Kata kunci: Diabetes melitus tipe 2, evaluasi penggunaan obat, nefropati diabetik

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Introduction

Type 2 diabetes mellitus (T2DM) is a type of diabetes mellitus (DM) which reached 90% of all other types.[1,2] Approximately 422 million adults living with diabetes and it has caused 1.5 million deaths in 2012.[3] In Indonesia, 1.5% or an estimation of 3.7 million people living with diabetes.[4] The hallmark of T2DM is insulin resistance and inadequate insulin secretion, although the role of glucagon excess cannot be underestimated.[5,6]

Common complication in T2DM patients is diabetic nephropathy (DN), since as many as 50% of patients with DM of more than 20 years' duration having this complication.[7,8] Multigenetic predisposition contributes to the development of DN. Hyperglycemia induces renal damage directly or through hemodynamic modifications. It induces protein kinase C activation, increases production of advanced glycosylation end products, diacylglycerol synthesis, glomerular hyperfiltration, shear stress, and microalbuminuria. These alterations contribute to an abnormal stimulation of resident renal cells that produce more TGF-β1, causes augmented extracellular matrix protein deposition (collagen types I, IV, V, and VI, fibronectin, and laminin) at the glomerular level, thus inducing mesangial expansion and membrane thickening.[8]

Both of the diseases account for significant morbidity and mortality, however appropriate treatment can reduce this events. Therefore, a study to evaluate the drug use in T2DM and DN inpatients is needed.

Methods

This study was conducted in one of hospitals in Tasikmalaya, Indonesia, in a period of March-June 2017. This study used descriptive cross-sectional observation with concurrent data retrieval. People from entire East Priangan, West Java come to this hospital to receive treatment for various medical conditions. Approval of the study was obtained from the National and Political Unity (Kesatuan Bangsa dan Politik, Kesbangpol) Tasikmalaya (No. 070/ 358/KKBP).

T2DM and DN patients with or without other comorbidities were included in the study. T2DM was defined and staged according to the guideline of the American Diabetes Association (ADA),[9] while DN was defined and staged according to the guideline of the Kidney Disease Improving Global Outcomes (KDIGO).[10] Guidelines of ADA (2017) and KDIGO (2012) were used to determine the appropriateness of drugs selection, meanwhile Drugs.com and Drugs Interaction Checker (Drugs.com) were used to determine doses accuracy and drugs interaction. Drugs.com is an online pharmaceutical encyclopedia which provides drug information for consumers and healthcare professionals primarily in the USA. The site contains a library of reference information which includes content obtained ftom Cerner Multum, Micromedex from Truven Health Analytics, Wolters Kluwer Health, U.S. Food and Drug Administration (FDA), A.D.A.M., Stedmans Medical Dictionary, American Society of Health System Pharmacy, Harvard Health Publications, Mayoclinic, North American Compendiums, and Healthday. In addition, this site is certified by the TRUSTe online privacy certification program.

Patients and quantitative characteristics data were collected from inpatients medical records, and by conducting direct interviews with patients and their observers. Qualitative data were collected from inpatient medical records and interview with their observers. Relevant data were extracted and recorded using a data collection form.

Results

Demography and quantitative analysis

Data of patients' characteristics were shown

Table 1 Patients' Characteristics

Characteristics	Diabetic Nephropathy		Type 2 Diabetes Mellitus	
	n	%	n	%
Gender				
Male	10	47.60	7	28.00
Female	11	52.40	18	72.00
Age				
0–2 years	0	0.00	0	0.00
2–10 years	0	0.00	0	0.00
11–17 years	0	0.00	0	0.00
18–40 years	1	4.80	3	12.00
41–65 years	12	57.10	12	48.00
>65 years	8	38.10	10	40.00
Length of Care				
<3 days	0	0.00	1	4.00
3–5 days	7	33.30	10	40.00
6–15 days	11	52.40	14	56.00
16–30 days	2	9.50	0	0.00
>30 days	1	4.80	0	0.00
Complications				
1 Complication	5	23.80	8	32.00
2 Complications	8	38.10	12	48.00
3 Complications	5	23.80	4	16.00
4 Complications	2	9.50	1	4.00
5 Complications	1	4.80	0	0.00
6 Complications	0	0.00	0	0.00
Insurance Status				
General	4	19.00	3	12.00
National Health Insurance (BPJS)	16	76.20	20	80.00
Jamkeskinda	1	4.80	2	8.00
Home Discharge Status				
Improved	19	90.50	23	92.00
Death	2	9.50	2	8.00
Total	**21**	**100.00**	**25**	**100.00**

in Table 1. The total of female DN and T2DM patients (52.4% and 72%, respectively) were more than that of male (47.6% and 28%, respectively), and this result was in line with Riskesdas (2013).[4] It was also found that patients with age interval of 41–65 years old were more common to suffer from DN and T2DM (57.1% and 48%, respectively). The length of care of both DN and T2DM patients were mostly 6–15 days. However, two of DN patients received 16–30 days and one received >30 days length of care, meanwhile none of T2DM patients received more than 15 days. Both DN and T2DM patients mostly had 2 complications (38.1% and 48%, respectively) and had BPJS/National Health Insurance (76.2% and 80%, respectively). Home discharge status of DN patients reached 90.5% of improved and 9.5% of death, while of T2DM patients reached 92% of improved and 8% of death.

The use of generic drugs in patients with DN and T2DM reached 68.7% and 65%, respectively. The most commonly used of the dosage form and administration route in DN was an injection (49.7%; 59.7%) followed by

Table 2 Quantitative Analysis of Generic-Non-generic, Dosage Form and Administration Route of Drugs

Disease	Diabetic Nephropathy		Type 2 Diabetes Mellitus	
	n	%	n	%
Generic/Non-generic Drugs				
Generic	445	68.70	470	65.00
Non-generic	203	31.30	253	35.00
Dosage Form				
Tablet	251	38.70	326	45.10
Injection	322	49.70	298	41.20
Infusion	65	10.00	74	10.20
Capsule	6	0.90	8	1.10
Suspension	1	0.20	5	0.70
Syrup	3	0.50	11	1.50
Cream	0	0.00	1	0.10
Administration Route				
Oral	261	40.30	350	48.40
Intravena	370	57.10	292	40.40
Intramuscular	17	2.60	80	11.10
Topical	0	0.00	1	0.10
Total R/	**648**	**100.00**	**723**	**100.00**

tablet/oral (38.7%; 40.3%). On the other hand, in T2DM, the most commonly used dosage form and administration route was tablet/oral (45.1%; 48.4%) followed by injection (41.2%; 51.5%) (Table 2).

Evaluation of appropriateness of drugs selection on T2DM and DN patients was done according to the guidelines of ADA and KDIGO.[9, 10] Appropriateness of drugs selection on T2DM was 100%, while appropriateness of drugs selection on DN only reached 85.6% (Table 3). Inappropriate drugs selection found in this study included ketorolac, ranitidine, folic acid, amlodipine, and potassium containing drugs.

Doses accuracy reached 100% on T2DM patients and only 92.1% on DN patients (Table 4). Inaccuracy of doses found in ranitidine, tranexamic acid, and metoclopramide.

Analysis of drugs interaction was done using drug interaction checker (drugs.com), and the result showed that drugs interaction on DN and T2DM patients mostly classified as moderate (64.1% and 58%, respectively). Result of drugs interaction analysis is shown in Table 5.

Discussion

Patients' characteristics showed the frequency of female T2DM and DN patients was higher than male. This might happen due to implication on the development of T2DM in female patients. Female tends to be more obese than male, and obesity is a major factor to the development of T2DM via impaired glucose tolerance.[11,12]

The high percentage of T2DM was directly

Table 3 Classification of Appropriate Drugs Selection

Disease	Appropriate (%)	Inappropriate (%)	Total (%)
Diabetic Nephropathy	85.60	14.40	100.00
Type 2 Diabetes Mellitus	100.00	0.00	100.00

Table 4 Classification of Doses Accuracy

Disease	Accurate (%)	Inaccurate (%)	Total (%)
Diabetic Nephropathy	92.10	7.90	100.00
Type 2 Diabetes Mellitus	100.00	0.00	100.00

proportional to that of DN. Hyperglycemia is a major factor to the development of kidney disease via mesangial expansion and membrane thickening.[8] In addition, age factor also contributes to the development of DN and T2DM usually over the age of 40.[13] Another study revealed that age related impairment of beta cell pancreatic was marked by insulin resistance (increased adiposity), decreased lean muscle mass (sarcopenia), mitochondrial dysfunctions, hormonal changes, increased oxidative stress and inflammation, changes in dietary habits, reduced physical activity and impairment of insulin secretion due to the mitochondrial dysfunction; reduced GLUT2 levels; accumulation of advanced glycation end products; telomerase deficiency and reduced telomere length; reduced expression of β2-adrenergic receptors; impaired Ca++ handling; reduced response to the GLP-1 stimulation; increased autophagy; reduced expression of beta-cell-specific genes and transcription factors such as PDX-1.[14] Based on the result of previous studies, hyperglycemia that occured developing into DN in 50% patients with T2DM of more than 20 years.[7,8] An increase in the number of elderly people in the future will make the diseases happen more commonly.

DN patients are commonly having anemia as complication which related to erythropoietin deficiency,[15] while in T2DM, diabetic ulcer complication found more common (12,4%) which related to neuropathy, trauma, deformity, high plantar pressure and peripheral arterial disease.[16] Diabetes mellitus exhibited more prevalence of infection caused by defects in immunity (low complement factor,[4] decreased cytokine response) and decreased function (chemotaxis, phagocytosis, killing) of polymorphonuclear cells and monocytes/ macrophages).[17] However, death caused by DN is more common than T2DM, possibly due to comorbidity that is kidney impairment. Microalbuminuria and macroalbuminuria increase mortality on any cause in diabetes mellitus and patients with proteinuria have a 40 times higher relative mortality rates.[18,19]

Length of care of both disease in the hospital will vary depend on several factors, such as institutional factors, the severity of the disease, social factors, psychological factors, adherence and nutritional status.[20,21] Length of care was associated with high cost and burden on family of the patients.[20] National health insurance helps lower the cost of health burden of patients/family, and subsequently increases the patients' quality of life. The participants of national health insurance are required to pay dues every month with a different amount based on each class.[22] Low economic families who cannot pay the dues are covered by Jamkeskinda, a healthcare insurance by regional government. A total of 19% DN patients and 12% T2DM patients were general patients, that is, people

Table 5 Classification of Drugs Interaction

Disease	Major		Moderate		Minor		Total (%)
	n	%	∑	%	n	%	
Diabetic Nephropathy	20	13.80	93	64.10	32	22.10	100.00
Type 2 Diabetes Mellitus	8	7.20	65	58.00	39	34.80	100.00

who used their own money to pay their medical bills and not covered by National Health Insurance in order to avoid queuing, meet service satisfaction and be able to use patent drugs, even though it is proven that generic drugs have the same efficacy and safety as brand name products.[23,24] Therefore, it is necessary to improve the service so that more patients willing to have national health insurance coverage.

The result of qualitative analysis showed that there was an inappropriate, inaccuracy doses and drug interaction potential. The inappropriate of drugs selection found includes ketorolac, ranitidine, folic acid, amlodipine, and potassium containing drugs. Ketorolac is one of the Non-Steroidal Anti-inflammatory Drugs (NSAIDs) group as an analgetic. Ketorolac is contraindicated in patients advanced renal impairment or stage 4 and higher.[25,26] In addition, NSAIDs on T2DM and DN patients increase cardiovascular and nephrotoxicity risk,[26–28] while all patients with DN have hypertension. Another study revealed that even a short treatment with NSAIDs could increase the risk for death; three-fold of myocardial infarction during an acute respiratory infection by oral and seven-fold by parenteral.[29,30] To avoid the adverse effect of NSAIDs, tramadol, paracetamol or their combination is a potential alternative analgesic for kidney impairment.[26]

Ranitidine is H-2 receptor antagonist for acid-related disorder. It is inappropriate since this drug is used in thrombocytopenia patients. Ranitidine is known as one of the drugs that induced or associated with thrombocytopenia through drugs promote tight binding of an antibody to a membrane glycoprotein and cause platelet destruction in patients with drug sensitivity.[31,32] In addition, ranitidine is contraindicated for thrombocytopenia (hypersensitivity).[33,34]

Folic acid is essential for DNA and RNA synthesis and repair. Moreover, folic acid is also important for making red blood cell. The inappropriate of folic acid for anemia in DN patients was not commonly caused by folic acid deficiency, but iron and erythropoietin deficiency and hyperresponsiveness.[35] Thus, folic acid administration for DN patients may be inappropriate. Iron and/or erythropoietin may be more beneficial for DN patients.

Amlodipine belongs to calcium channel blockers (CCBs) group for hypertension treatment. However, amlodipine is considered inappropriate since KDIGO clinical guideline[10] recommends angiotensin converting enzyme-inhibitor (ACE-I) or angiotensin receptor blocker (ARB) for DN patients. Moreover, CCBs effect in renal disease are not clearly defined. Renin-angiotensin axis blocking drugs are more effective than CCBs at reducing proteinuria, but the combination of CCBs and renin-angiotensin axis blocking drugs may be beneficial in improving renoprotective effects of ACE-I and ARB administered alone or combined with diuretics.[36] The use of potassium containing drugs is inappropriate due to electrolyte levels of potassium patients experiencing hyperkalemia that may result in sudden death from cardiac arrhytmias.[37]

Inaccuracy of doses (overdoses) reached a total of 7.9% of DN patients, and it was found in ranitidine, tranexamic acid and metoclopramide. It is necessary to adjust the dosage on ranitidine used on eGFR <50 mL/min (oral dosage form is 150 mg, every 24 hours; 50 mg IM/IV, every 18–24 hours), tranexamic acid used on serum creatinine >5.7 mg/dL (650 mg orally, once a day) and metoclopramide eGFR <40 mL/min (initial dose is 50% of the usual recommended dose).[38–40] Overdoses will increase an adverse effect, kidney failure progressivity, failure of medication and life threatening.

Drug interaction potential is classified by major, moderate and minor. Major interaction results in multiple effect interactions, such as hyperkalemia, seizure, hypokalemia,

hypomagnesemia, increasing the drugs concentration on blood, precipitation of ceftriaxone salt, kidney failure, inflammation, bleeding, ulceration and gastrointestinal perforation. Moderate interaction have been found in high number resulting multiple effect interaction such as hypokalemia, decrease glomerulus filtration rate, hypotension, hypovolemia, increasing drugs concentration on blood, hyperglycemia, hypoglycemia, nephrotoxicity, hypomagnesemia, angioedema, decrease tubular secretion, increase/decrease drugs concentration on blood, the decrease of bioavailability and hepatotoxicity. General management of major and moderate interaction is by avoiding combination drugs, and on minor interaction by assessing risk of alternative drugs,[41] not only through a close monitoring and risk and benefit ratio consideration.

Conclusion

Based on the result of this study, there was an inappropriate drug selection in DN patients, an inaccuracy of dose in DN patients and a high percentage of drugs interaction on moderate classification on both diseases. This problems may result in inadequate outcome of therapy and can be harmful to the patients. It is necessary to optimize the role of pharmacist as a part of the healthcare team in the patients' room in medication therapy management application as a preventive way in order to increase the patients' quality of life.

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Conflict of Interest

Authors declare that there is no conflict of interest regarding the publication of this paper.

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