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Rational use of Metoprolol: The Relationship of Its Blood Concentration to Patient Compliance, Poor Quality Medicines and Side Effects

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ABSTRACT

Background: Patients with cardiovascular diseases might be poorly educated regarding the rational use of their drug treatment, such as dealing with missing doses, relationship to food, and potential side effects. In addition, many poor quality medications are available in our drug market that might differ in their efficacy and safety profiles.

Aim: Metoprolol, a commonly used drug in our local medical practice, is to be investigated through measuring its blood concentration at one point of time after achieving the steady state, and to correlate blood concentration with compliance, side effects and the quality of brand products they are using.

Methods: Measurement of levels of metoprolol (by scanning spectrometry) in blood samples taken from patients at their visits to the consultation clinics in Thi-Qar during the period October 2014 to April 2015 was made. Their blood concentrations was correlated with compliance, side effects and the quality of the drugs they were using. A questionnaire containing patient demographic information, type disease, type of drugs, trade names, and a check-list of potential side effects, was used.

Results: Out of the 56 patients who were treated with different preparations and dosage regimens of metoprolol, 53 patients were within the reported therapeutic range of metoprolol plasma concentration (0.035-0.5µg/ml). The two brand metoprolol products used were found interchangeable with no significant difference in their achieved plasma concentration. The most frequent adverse effects associated with the use of metoprolol were tiredness followed by dyspnea and bradycardia. There is no difference between the two brand products of metoprolol in relation to the frequency of side effects. Around 90% of patients using metoprolol were not aware of the proper action to be taken when they miss a dose. 23.2% of patients who reported missing one or more doses did not take any action till the next dose.

Conclusion: Availability of more than one brand product of metoprolol and other drugs need to be investigated in terms of their blood levels and occurrence of adverse effects especially when these drugs are used for long duration to test their interchangeability. Patient awareness of the proper use of drugs is necessary in order to increase effectiveness of their treatment and decrease potential side effects.

Key words: Metoprolol, Plasma concentrations, Adverse effects, Brand products, Proper use.

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INTRODUCTION

There are limited number of studies that focus on therapeutic monitoring of beta-blockers. The advantage of measuring plasma level of anti-arrhythmic drugs is in studying compliance and toxicity.[1] It is also required for optimizing the dosage of these drugs since there is a relationship between plasma drug level and their pharmacological effects.[2]

Measurement of plasma level of anti-arrhythmic drugs can be used as a guide for treatment when high doses or when drugs with long half-lives are used. In addition, it may be required in case of treatment failure that may occur because of poor compliance, and in determining drug toxicity.[3] Other objectives for measuring plasma level include: determination of patient adherence to treatment, assessment of risk-benefit ratio of changing the dose and the presence drug - drug interaction.[4]
Therapeutic drug monitoring of beta blockers can lead to more therapy individualization and will improve safety with more cost effectiveness.[5]

Wanzhu et al[6] studied 80 patients treated with metoprolol for 6-12 months and more and found that plasma concentration of metoprolol can be used to measure patient adherence to therapy which is

necessary to avoid deterioration of patient illness cuts down extra expenses of visiting emergency departments. The aim of the present study is, therefore, to correlate metoprolol blood concentration with patient compliance, side effects and the quality of brand products they are using.

SUBJECTS

Patients with atrial fibrillation on treatment with metoprolol succinate and attending cardiology consultation clinics at Thi-Qar were recruited during the period of October 2014 to April 2015.
Both male and female patients with atrial fibrillation, 30 to 65 years of age, were recruited for this study. They should be on treatment with metoprolol succinate for at least 3 months on the same brand name (to allow enough time for a steady state to be reached and for potential side effects to appear). Patients gave their consent to participate in this study, and the side effects were followed according to a check-list of expected and potential side effects. Their clinical responses were assessed by their treating physicians.

METHODS

A questionnaire was prepared containing patient demographic information, type of disease, its duration, type of drugs used with their doses, duration of treatment, trade names, and a check-list of side effects that may be associated with its use.
A single blood sample was taken from each patient at his attendance to consultation clinics, for drug level measurement. Metoprolol blood

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concentration was cross-matched with drug effect, side effects and quality of drugs they were using. Metoprolol concentrations was measured by using UV-Visible double beam scanning spectrometer (T90+ UV/VIS Spectro-meter PG Instruments, UK) consisting of a double beam optical system, selectable scan speed system, photomultiplier tube detector, tungsten halogen and deuterium arc lamp, and computerized system controller (UV-Win GLP). Quantification was achieved by measurement of absorbance using UV-Win GLP software quantitative analysis. The maximum absorbance of a standard solution was found at a wavelength of 278 nm. This spectrophotometric scanning method of metoprolol succinate was, based on the method described by Badulescu et al.[7]
This method had succeeded to give a linear calibration curve with a minimum detection level of 0.01 µg/ml.

STATISTICAL ANALYSIS

Comparisons between measurements were made by analysis of variance (ANOVA) using SPSS (Statistical Package of Social Sciences) version 20. T-test was used to test significance of changes between different variables. Exact Fisher test was used for categorical data. A difference was considered statistically significant for p value of 0.05 and less.

RESULTS

Fifty six adult patients with atrial fibrillation and attending consultation clinics and Al-Husain teaching hospital (Thi-Qar) from October 2014 to April 2015 and treated with different regimens of metoprolol succinate were included in the present study. They were divided into two groups according to the trade name of metoprolol succinate they were using. They were then divided into three subgroups according to dose and frequency of their
metoprolol treatment. Patients included were chronically treated with metoprolol succinate for a mean period of 1.08± 0.86 years, ranging from 3 months to 3 years to ensure that patients had reached the steady state.
Plasma metoprolol concentration in blood was measured and divided into two groups according to the brand product of metoprolol succinate tablet used by those patients. The majority of patients (94.6%) were found to be within the established range of metoprolol plasma concentration (0.035 -0.5µg/ml). The mean plasma concentration was 0.19 ± 0.11µg/ml (ranging from 0.007 to 0.65µg/ml). One patient exhibited a higher than therapeutic (0.65µg/ml) and two patients had sub-therapeutic levels (0.007 and 0.02µg/ml).

The mean plasma metoprolol succinate concentration of brand product-1 was found to be 0.18±0.09µg/ml while that for brand product-2 was 0.20±0.12µg/ml (Table 1 and figure 1)

The adverse effects were monitored through directly interviewing patients according to a check-list of known and potential adverse effects of brand metoprolol products with a help from their treating physician (A brand is a type of product manufactured by a particular company under a particular name). Twenty six adverse effects were reported by 28 patients in association with use of brand metoprolol product-1 concurrently

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with other drug treatments (92.8%). This is compared with 25 adverse effects associated with use of brand metoprolol product-2 in 28 patients (89.3%) (Table 2).

The reported adverse effects varied from cardiovascular, gastrointestinal, respiratory and others which were associated with the use of the two metoprolol brand products taken concomitantly with different other drug treatments. When different doses and frequencies are grouped together, the two products were comparable in the incidence of these adverse effects (Table 2).

The most frequents adverse effects reported by patients using metoprolol or by their treating physicians were tiredness followed in descending order by dyspnea, bradycardia, constipation, dizziness, nausea, headache and cold extremities.

When adverse effects were compared between those caused by 100mg once daily and 50mg twice daily groups, results were not significantly different.

Table 1 Plasma concentrations of metoprolol succinate in patients treated with two brands products of metoprolol succinate.

Groups	N	Plasma concentration (µg/ml)	Duration* (years)	Time** (hours)
Brand metoprolol product 1 (50 mg) once daily	10	0.12±0.05	1.03 ± 0.97	14.3± 10.37
Brand metoprolol product 2 (50 mg) once daily	11	0.10±0.04	1.31 ± 0.85	9.45± 1.86
Brand metoprolol product 1 (50 mg) Twice daily	9	0.20 ± 0.05	0.95± 0.93	8.66± 3.14
Brand metoprolol product 2 (50 mg) Twice daily	13	0.23 ± 0.08	1.03± 0.89	9.58 ± 3.36
Brand metoprolol product 1 (100 mg) once daily	9	0.31± 0.13	1.16± 0.96	18.3 ±8.64
Brand metoprolol product 2 (100 mg) once daily	4	0.29± 0.14	0.5± 0.35	12± 1.41
Total	56	0.19 ± 0.11	1.08± 0.86	11.5±0.88

N = number of patients treated with metoprolol, *Duration of metoprolol use,
** Time of blood sampling after last metoprolol dose. Data are presented as means

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± SD. Differences between similar groups of the two products are not significant (P = 0.461).

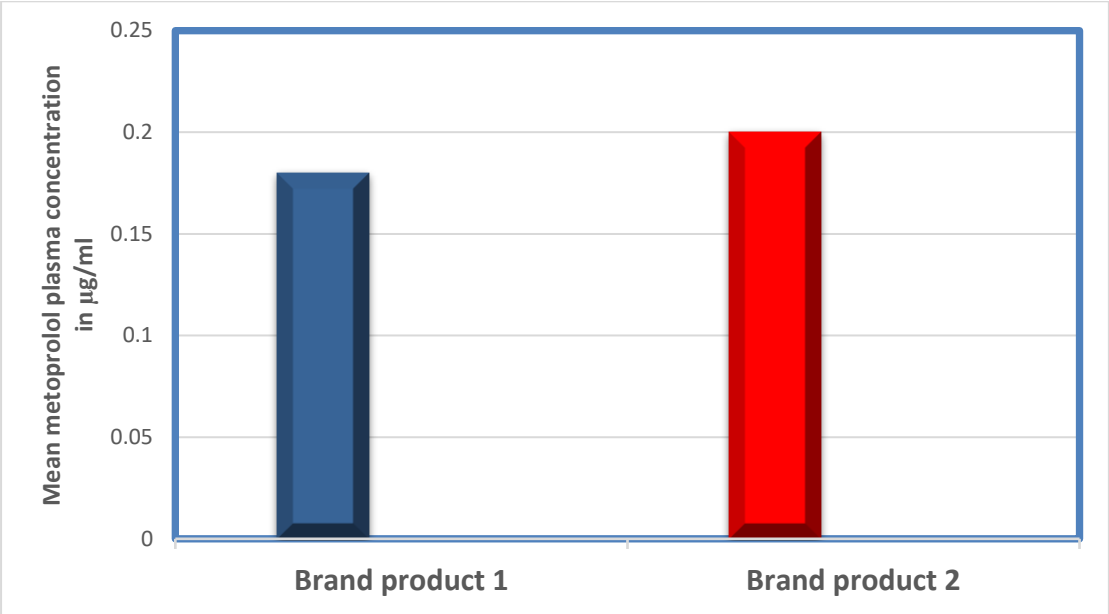

Figure 1 Mean plasma concentration of the two metoprolol succinate brand products (P = 0.461).

Table 2 Types of adverse effects associated with the use of metoprolol brand products (1 and 2) when used concomitantly with other drugs.

Groups	N	Types of adverse effects							
		Tired-ness	Dyspnea	Brady-cardia	Consti-pation	Dizzi-ness	Nausea	Head-ache	Cold extremi-ties
Brand metoprolol Product-1	28	14 50%	11 39.3%	10 35.7%	6 21.4%	5 17.9%	5 17.8%	2 7.1%	3 10.7%
Brand metoprolol product-2	28	12 42.9%	13 46.4%	9 32.1%	8 28.6%	5 17.9%	4 14.3%	3 10.7%	2 7.1%
Total	56	26 46.4%	24 42.9%	19 33.9%	14 25%	10 17.9%	9 16.1%	5 8.9%	5 8.9%
P value*		0.600	0.597	0.783	0.546	0.351	0.722	0.647	1.00

* Statistical significance between the two brand products

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All the 56 patients taking part in the present work were found to take their medications in right manner regarding food (taking metoprolol after meal as prescribed). Fifty of them (89.3) were not aware what to do if they missed a dose. 13 (23.2%) of the 56 patients reported to have missed one or more doses and their action was to take no action and wait for next. No doubling of the next dose was reported. The rate of missing a dose in a once daily regimens was 30.8%, while for twice daily regimens 69.2%. The difference is statistically significant (P= 0.011).

The rate of missing a dose is significantly correlated with the level of education. In those whose education above primary school (n=27), the rate was 23.1%, while education with primary school level and less (n=29), the rate was 76.9% (P = 0.018).

DISCUSSION

Assessment of plasma levels of different brands of metoprolol as the case in our present study, is required to compare between more than one brand product of metoprolol in order to assess their interchangeability and it is an attempt to discover defective products. In addition, patient awareness of some important aspects of beta blockers use e.g. patient reaction to missing doses which is an important factor that can affect patient's health, are investigated. It had been shown that patients with heart failure when they had higher medical knowledge about their drugs and adhere to their treatments, there will be fewer visits to emergency departments with reduction in their medical expenses.[8]

The plasma concentrations at steady state of two brand products of metoprolol used in the present study was found to be 0.12±0.05 and 0.10±0.04 µg/ml respectively after using 50mg of each of the two products once daily with no statistically significant difference between them. Bengtsson et al[9] also found the mean plasma level of metoprolol given as once daily 50mg dose to be 0.1 µg/ml after reaching the steady state.

A previous comparison between other two brand products of metoprolol succinate; Betalok ZOK (Astra Zeneca AB) and Beto ZK (Sandoz GmbH) showed that both formulations were bioequivalent and interchangeable with no difference in the incidence of adverse effects.[10]

In present study, no significant difference was found between the two metoprolol brand products in terms of serum concentration and adverse effects that might be associated with their use. The reported adverse effects are not necessarily caused by metoprolol. Such association could be a casual association due to concomitant use of other drugs. One common adverse effect associated with use of both products is tiredness which is a

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common complaint reported by around 50% of patients. Interaction between metoprolol and other drugs used at same time might have contributed to this high percentage. Examples of such drugs are omeprazole and chlor-diazepoxide. Omeprazole can cause fatigue through hypomagnesaemia when used chronically for more than 3 months.[11] while chlordiazepoxide causes fatigue through inhibition of central nervous system.[12]

It had been shown that the rate of missed doses was significantly higher with twice daily metoprolol regimen when compared with once daily betaxolol regimen.[13] In the present study, the percent of patients who forgot their doses, was 30.8% with single daily metoprolol dose regimens. This is compared with 69.2% with twice daily regimens (P = 0.011). All patients who missed metoprolol doses, did not take the missed dose when they remembered it. When the intake of drugs in relation to food was investigated in the present study, the results showed that patients took their medications in the right manner regarding food. Spiers et al[14] found that majority of elderly patients were having good understanding of their medications. In addition, 80% of patients studied by Stone et al[15] had complete understanding of instructions regarding their medications in relation to meals.

When patients were assessed according to their level of education (above and below primary school levels) there was a significant difference between the two groups regarding their adherence to treatment. The group with level of education above primary school had lower rate (23.1%) of forgetting their doses while those with lower level of education, the rate was much higher (76.9%). This points to the importance of patient education regarding proper use of their medications particularly patients of low education. Several studies pointed to a significant effect of patient education level on adherence to instructions on therapy.[16, 17]. Spectrophotometric methods can be used to measure drugs, not only in drug formulations but also in body fluids such as saliva, urine and blood. For example, it had been used to measure theophylline in saliva and urine with minimum detection concentration of 0.07 µg/ml.[18] and for pregabalin in urine, with minimum detection concentration of 0.08 µg/ml).[19]

Finally, it can be concluded that the majority of patients who were treated with different formulations and dosage regimens of metoprolol succinate were found within the reported therapeutic range of metoprolol plasma concentration. The two brand metoprolol products used by those patients were interchangeable with no significant difference in their achieved plasma concentration and adverse effects. Around 23% of patients who reported missing one or more doses did not take any action till the next dose. The frequency of missed doses was

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significantly correlated with low level of education and dose frequency.

Availability of more than one brand products need, therefore, to be investigated in terms of their blood levels and incidence of adverse effects to find out whether these brand products are bioequivalent and interchangeable. This is particularly true when these brands differ in their costs. Patient education about the proper use of drugs is necessary in order to increase effectiveness of their treatment and decrease their adverse effects.

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الاستعمال الرشيد للميتوبرولول: العلاقة بين تركيزه في الدم مع التزام المريض والنوعية غير الجيدة للأدوية والتأثيرات الجانبية

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الملخص

خلفية الدراسة

المرضى المصابين بأمراض القلب والاوعية الدموية قد يكونوا أقل معرفة بالاستعمال الرشيد للادوية التي يستعملونها مثل التعامل مع الجرعات المنسية والعلاقة مع الطعام والاثار الجانبية المحتملة والتي قد تنتج عن استعمالهم لهذه الادوية. إضافة الى أن العديد من الادوية ذات النوعية الرديئة متوفر في أسواقنا الدوائية المحلية والتي يمكن أن تسبب اختلافاً في أنماط فعاليتها وسميتها.

الهدف

الهدف هو تقصي دواء يستعمل لمعالجة المشاكل القلبية في الممارسة الطبية المحلية وهو الميتوبرولول عن طريق قياس تراكيزه في الدم في وقت منفرد بعد وصول تراكيزه الى الحالة المستقرة، ولايجاد العلاقة بين التركيز في الدم والاثار الجانبية ونوعية المنتج التجاري المستعمل.

طرائق العمل

تم قياس مستوى الميتوبرولول (بواسطة المطياف الماسح) في عينات الدم المأخوذه من المرضى عند زيارتهم للعيادات الاستشارية في ذي قار خلال المدة بين تشرين الاول ٢٠١٤ وتموز ٢٠١٥.كما تم البحث عن علاقة تراكيز هذه الادوية ومطاوعة المريض في أخذها ومع التأثيرات الجانبية ونوعية الادوية التي يستعملونها. وهناك استبيان تم ملؤه لكل مريض يحتوي على معلومات عن المرضى ونوع المرض ومدته والادوية المستعملة لعلاجه مع جرعاتها ومدة استعمالها واسمائها التجارية بالاضافة الى قائمة مراجعة للتأثيرات الجانبية المحتملة.

النتائج

من بين ٥٦ مريضاً عولجوا بمستحضرات ونظام جرعات مختلفة للميتوبرولول، هناك ٥٣ مريضاً كان تركيز المتوبرولول في مصل الدم ضمن المدى العلاجي المعروف. وقد وجد أن النوعان التجاريان للمتوبرولول قابل للمبادلة ولا يوجد بين تركيزهما في مصل الدم فرق معتد. إن الاثار الجانبية الأكثر حدوثاً والتي صاحبت استعمال المتوبرولول هي: التعب يتبعه ضيق النفس وبطيء ضربات القلب والامساك والدوخة والغثيان وبرودة الاطراف والصداع. ولا يوجد فرق بين المنتجين التجاريين الاثنين للمتوبرولول في نسبة حدوث الاثار الجانبية. كما أن حوالي ٩٠% من المرضى لم يكونوا على دراية بالفعل الصحيح الذي يجب اتخاذه عندما ينسون جرعة معينة.

الاستنتاج

أن توفر أكثر من منتج تجاري واحد للمتوبرولول وأدوية أخرى يحتاج التقصي عنه بما يتعلق بمستوياتهم في الدم وحدوث الاثار الجانبية وبخاصة عند استعمال هذه الادوية لمدة طويلة للتأكد من امكانية استعمالهما كبدائل والبحث عن الادوية المغشوشة. إن دراية المريض بالاستعمال الصحيح للأدوية ضروري لزيادة فعالية تلك العلاجات والتقليل من الاثار الجانبية المحتملة.

مفتاح الكلمات

ميتوبرولول، التراكيز، الاعراض الجانبية، العلامة التجارية، الاستعمال الامثل