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The awareness of prodrugs interactions among Medical practitioners in Khartoum, Sudan

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ABSTRACT

Prodrugs are form of medications in which the drug is given as inactive parent compound, and then activated in the body by various metabolic processes, after administration. The main objective of this study was to assess the awareness about the cardiovascular prodrugs and their interactions among medical practitioners and to assess the relationship between the physicians' awareness, medical professional and years of experience. Method: The study was cross sectional hospital based study, conducted among physicians working in three of Khartoum state hospitals. Data was collected via structure questionnaire. This is study surveyed 196 medical practitioners, 109 (55.6%) were male and 87 (44.4%) were female, mean for the age was 29.04. more than two third (73%) of the medical practitioners knew prodrug. Concomitant prescribing of proton pump inhibitors with Clopidogrel (prodrug) was about half 97 (49%) of total medical practitioners surveyed, followed by Losartan and Metronidazole 81 (41.3%). More than half (51%) of the respondents answered correctly that Enalapril is cardiovascular prodrug. The overall knowledge of prodrugs interaction effect on therapeutic level was very low ranged from (15.85 %- 37.25%). The most frequent prodrug prescribed on daily basis was Statins followed by Clopidogrel. It concluded that awareness regarding prodrug is low among medical practitioners. The awareness and the knowledge of the medical practitioners about prodrug increase with age, and with their professional medical positions.

Introduction

Prodrugs are a form of medications in which the drug is given as inactive parent compound, which is then activated in the body by various metabolic processes, often catalyzed by the cytochrome P450 (CYP) enzymes to yield the active form responsible for the clinical effects (1). A prodrug serves as a type of precursor to the intended drug, Prodrugs can be used to improve how the intended drug is absorbed, distributed, metabolized and excreted.

Prodrugs are often designed to improve oral bioavailability in cases where the intended drug is poorly absorbed through the gastrointestinal tract e.g. Bacampicillin is prodrug of Ampicillin increase the oral bioavailability (98–99%), whereas that of Ampicillin is <50% (2). Also Enalaprilat is poorly absorbed from the gastrointestinal tract (<10%), but absorption of the prodrug Enalapril is greatly improved (60%). (3). A prodrug may also be used to improve the selectively of the intended drug interactions with cells or processes that are not its intended target. This reduces the adverse or unintended effects of the intended drug, especially important in treatments like chemotherapy (4, 5), which can have severe unintended and undesirable side effects. According to the pharmacokinetic characteristics of the prodrug a lot of precautions should considered when prescribing prodrugs to avoid treatment failure.

Drug-drug interactions are a noteworthy cause of adverse drug reactions, but in most cases they can interact through inducing or inhibition of activation of metabolic enzymes. Prevention or enhancement of this activation process can reduce or increase the clinical effects of prodrugs.

Losartan is a widely used Angiotensin II receptor antagonist, which is oxidized to its active carboxylic acid metabolite E-3174 by CYP2C9. The formation of the active metabolite may be prevented by the CYP2C9 inhibitors, for example Amiodarone, Fluconazole and Metronidazole. (3). Coadministration of a CYP2C9 inhibitor and Losartan was found in 19.4% of all Losartan treatment period; in study done by Tuire Tirkkonen (6) conclude that: Coadministration of drugs that potentially result in inhibition of prodrug activation present a common and unrecognized source of irrational prescribing.

Statins, are HMG-CoA reductase inhibitor, widely used in the treatment of hypercholesterolaemia. The oxidative biotransformation of statins is mediated primarily by CYP3A4. CYP3A4 inhibitors like cyclosporine, Itraconazole, ketoconazole, Erythromycin, Clarithromycin, can elevate the plasma concentration of HMG-CoA reductase inhibitory activity cause myopathy (7-11). In the other hand many diet has effect on drug famous example is Grapefruit juice (GFJ) which contains a number of naturally occurring furanocoumarin derivatives that irreversibly inhibit cytochrome P450-3A (CYP3A) enzymes important in human drug metabolism, possibly leading to enhanced clinical effects or adverse reactions.(12).

Clopidogrel, a second-generation thienopyridine that inhibits platelet aggregation, is a mainstay, along with aspirin, in the management of patients with coronary artery disease (13).

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Clopidogrel is an inactive prodrug that requires hepatic bioactivation via several cytochrome P450 enzymes, including CYP2C19. The active metabolite irreversibly inhibits the platelet ADP receptor, P2Y12. Many studies (14-16) documented that the risk of re-hospitalization for MI, for patients using Clopidogrel with a proton pump inhibitors was 93% higher than did patients receiving Clopidogrel alone.

The main objective of this study was to assess the awareness about the cardiovascular prodrugs and their interactions among medical practitioners and to assess the relationship between the physicians' awareness, medical professional and years of experience. On this research we are more concern about cardiovascular prodrugs Clopidogrel, Losartan, Enalapril and Statins.

Materials and method

This cross sectional hospital based study, carried in three governmental hospitals in Khartoum state: Alshaab hospital (specialized hospital for cardiovascular diseases), Khartoum teaching hospital (the central hospital in Khartoum), and Sudan heart center. Consultants, registrars, medical officers and house officers working in study areas were surveyed. Sample of 196 medical practitioners were selected as non random convience sampling. The study was conducted during the period May 2013 – September 2013.The data was collected by specific designed structured questionnaire (self submitted questionnaire), the data were analyzed using (SPSS). Verbal consent was taken from medical directors to allow conducting the study.

Results

Of 196 medical practitioners completed the questionnaire, 109 (55.6%) were male and 87 (44.4%) were female. the mean for the age was 29.04, more than half of the respondents their age between 25-30 years.

Figure (1) shows that most of the respondents were medical officers followed by registrars, house officers and consultants. More than half (53. 1%) of respondents with experience of (0-2 years) and (27%) with experience of (3-5) years. The remaining between (6-15) years experience.

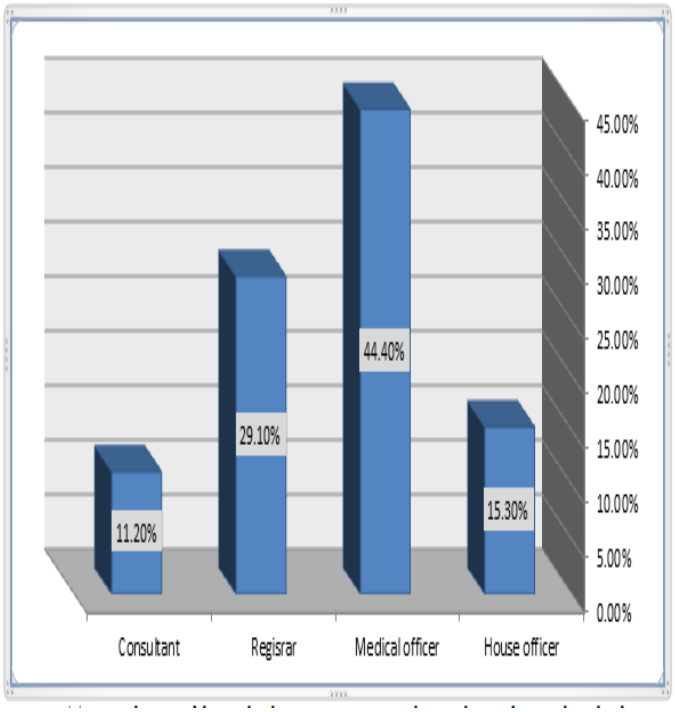

Figure (1).Distribution of the medical practitioners according to the professional medical position (n=196)

73% of respondents knew about prodrugs, and more than half (51%) of them answered correctly that Enalapril is cardiovascular prodrug. The most frequent prodrug prescribed on daily basis was Statins followed by Clopidogrel, while Enalapril was the lowest one prescribed.

Table (1) shows that physicians were prescribed combinations of drugs that have drugs interactions. Concomitant prescribing of proton pump inhibitors with Clopidogrel (prodrug) was about half 97 (49%) of total combinations prescribed, followed by Losartan (prodrug) and Metronidazole 81 (41.3%).

Table (1).The frequency and percentage for prescribing prodrugs interacting with other drugs.

Combinations	Yes	No	% Yes	% No
1. Clopidogrel & Omeprazole	97	99	49.5%	50.5%
2. Losartan & Metronidazole	81	115	41.3%	58.7%
3. Losartan & Amiodarone	45	151	23.0%	77.0%
4. Statin & Itraconazole	15	181	7.7%	92.3%

The overall knowledge of drug interaction effect on therapeutic level was very low ranged between (15.85%-37.25%) as shown in table (2). The awareness of respondents to concomitant Losartan and Amiodarone, Losartan and Metronidazole drug interaction was 18%, and 20% respectively. However they were more aware about concomitant of Clopidogrel and Omerprazole, and Statin and Itraconazole 30%, and 27% respectively.

Table (2).The awareness of prodrug interactions

	Correct answer	**Wrong answer**	**I don't know**
Combination of Losartan & Metronidazole	40 (20.4%)	43 (21.9%)	113 (57.7%)
Combination of Clopidogrel and Omeprazole	59 (30.1%)	53 (27%)	84 (42.9)
Combination of Losartan and Amiodarone	36 (18.4%)	21.9%) (43	117 (59.7%)
Combination of Grapefruit juice and Atorvastatin	73 (37.2%)	38 (19.4%)	85 (43.4%)
Combination of Statin and Itraconazole	53 (27.0%)	34 (17.3%)	109 (55.6%
Combination of Clopidogrel and Ginseng	31 (15.8%)	19 (9.7%)	46 (74.5%)

More than half (58%) of the respondents were aware that the liver impairment affects the Enalapril. Only 30% knew the exact pharmacological adverse reaction from co-administration of Clopidogrel and Omeprazole figure (2). There was significant relationship between the age and the awareness, as age increased awareness about prodrug increased ($P \geq 0.013$). There was interrelationship between professional position and awareness; there is significant difference between consultants and other positions in prescribing cardiovascular prodrugs ($P \geq 0.008$). Table (3) shows that there was also significant difference in the awareness of prodrug interactions among the medical

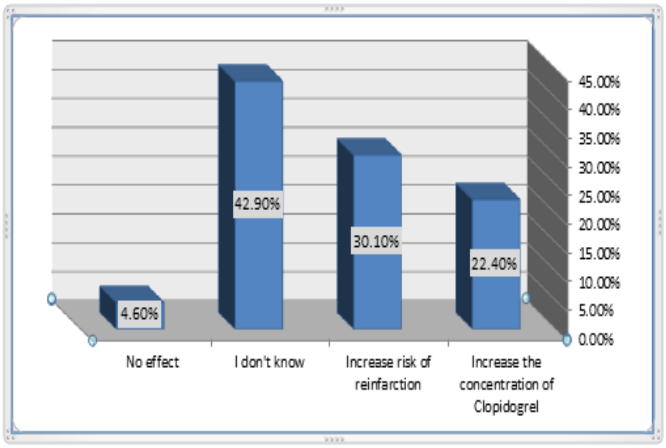

Figure (2). The awareness of the Clopidogrel & Omeprazole drug interactions (n=196)

practitioners according to their medical professional in case of the concomitant Clopidogrel and Omeprazole only 10.0% of the house officers were aware that Clopidogrel activation inhibited by Omeprazole, and increase the risk of rehospitalization and reinfarction in patient with MI, in contrast 26.4%, 35.1%, and 59.1% of the medical officers, registrar and consultants were aware.

Discussion

The correct use of a drug is determined by several important factors, some of them related to drug characteristics and other to patient profile. The awareness of drug characteristics includes contraindications, drug -drug interactions and warnings. Patient profile includes careful evaluation of the patient in order to consider possible risk factors, such as concomitant pathologies, and food habit to avoid drug diseases or drug food interactions. Prodrugs need special and additional precautions; because they have unique pharmacokinetic properties, thus the measurement of the prodrugs interactions highly needed among prescribers.

Our study was aimed to evaluate the awareness of prodrug knowledge among medical practitioners with varying degree of clinical experience. This is a new study, and there is no previous study was done similarly as to our knowledge.

of 73% of the medical practitioners were knew prodrugs, 60.7 % take precautions when they prescribe prodrug, and this is gap between the knowledge and the practice, which may lead to alterations on the efficacy of the prodrugs and probably adverse effects.

Most of the medical practitioners were prescribed Clopidogrel with Omerprazole, this may be due as many studies revealed to the high use of Clopidogrel as a combined with Aspirin to reduces recurrent cardiovascular events following hospitalization for acute coronary syndrome (ACS) for patients treated either medically or with percutaneous coronary intervention (PCI). On the other hand proton pump inhibitor (PPI) medications are often prescribed prophylactically with initiation of Clopidogrel, with the goal of reducing the risk of gastrointestinal tract bleeding while taking dual-antiplatelet therapy (13-15). Many of respondents also prescribed Losartan and Metronidazole and could be due to the wide use of Metronidazole in gastroenteritis (GE) and in suspected anaerobic bacterial infections.

Our study measures the awareness about prodrug interaction of cardiovascular drugs, because in many cases drug-drug interactions and drug-food interactions inhibit prodrug bioactivation and thereby have the potential to reduce the therapeutic efficacy . These interactions may be classified as ‘silent’ but could still be very important clinically, because of late identification and impaired preventive treatment of serious underlying conditions. (12 ,16). Table (2) indicate that one third and less of the respondents awarded about the interactions between combination of cardivascular drugs and other medications they prescribed, while slightly more the third (37%) award by drug – food interaction (Atrovastatin and Grape –fruit juice).

There was significant relationship between the age of prescriber and the awareness, medical practitioners above (40 years) take precautions when prescribe prodrugs more than younger practitioners (P = 0.013). There is also a relationship between the medical position and the awareness of prodrugs . Consultants significantly take precautions when they prescribe prodrug more than house officers, medical officers and registers (P ≥ 0.008).

Table (3). Relationship between professional position and awareness of prodrugs interactions

	Professional position								Total	P value
Combination of Clopidogrel and Omeprazole	House officers		Medical officers		Registrars		Consultants			
Increase risk of reinfarction(true)	3	10%	23	26.4%	20	35.1%	13	59.1%	59	0.000
Wrong answer	27	90%	64	73.6%	37	64.9%	9	40.9%	137	
Combination of Losartan and Amiodarone	House officers		Medicals officer		Registrars		Consultants			
Wrong answer	27	90%	72	82.8%	49	86%	12	54.5%	160	0.000
True answer	3	10%	15	17.2%	8	14.0%	10	45.5%	36	
Combination of Grapefruit and Atorvastatin	House officers		Medical officers		Registrars		Consultant			
True answer	6	20%	32	36.8%	24	42.1%	11	50%	73	0.011
wrong	24	80%	55	63.2%	33	57.9%	11	50%	123	
Combination of Statin and Itraconazole	House officers		Medical officers		Registrars		Consultants			
True	1	3.3%	21	24.1%	16	28.1%	15	68.2%	53	0.000
Wrong	29	96.7%	66	75.9%	41	71.9%	7	31.8%	143	

Our study revealed that consultant were better in knowledge of some prodrugs , interactions (such as Clopidogrel activation inhibited by Omeprazole, and increase the risk of rehospitalization and reinfarction in patient with post stent) than other professional groups which could be due to their higher periods of clinical learning and updates through symposiums, conferences etc.,

Limitation on this study, there are no literature review for this study so we can't compared our results with other similar studies, we think our study could be a database for other researches interested in this new topic.

Conclusion

The present study revealed that, awareness regarding prodrug is low among medical practitioners. The awareness and knowledge of the medical practitioners about prodrug increase with age, and with their professional medical positions. Further education through the development of guidelines and interactive educational materials is important and recommended during residency training. Enforcements and more emphasis in pharmacology teaching was recommend for under graduation pharmacology curriculum in medical schools.

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