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Full Length Research Paper

Determining potential drug-drug interactions between lopinavir/ritonavir and other antiretrovirals and prescribed daily doses in a section of the private health care sector in South Africa

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Lopinavir/ritonavir forms part of the antiretroviral therapy for the treatment of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). The aim of this non-experimental, quantitative drug-utilization study was to determine and identify potential drug-drug interactions between lopinavir/ritonavir and other antiretrovirals in general practitioners and specialists prescriptions with inappropriate prescribed daily doses. The study was performed on 49,995 (2005), 81,096 (2006) and 88,988 (2007) anti-retroviral (ARV) prescriptions claimed through a pharmacy benefit management company. Of the total 2,638 ARV general practitioners prescriptions and 472 specialist's prescriptions claimed with potential drug-drug interactions (DDIs), 505 (19.1%) were for general practitioners and 143 (30.3%) for specialists. Potential drug-drug interactions identified between lopinavir/ritonavir and other anti-retrovirals with inappropriate prescribed daily doses accounted for 88.9% (n = 449) for general practitioners and 98.6% (n = 141) for specialist's prescriptions. The highest percentage of anti-retroviral prescriptions with potential drug-drug interactions were between lopinavir/ritonavir at 1066.4 mg/264 mg and efavirenz at 600 mg average of prescribed daily doses with 61.4% (n = 276) for general practitioners and 38.3% (n = 54) for specialists, prescribed to patients between 19 and 45 years. The recommended standard adult dose for lopivavir/ritonavir is 400 mg/100 mg twice daily or 800 mg/200 mg once daily. The dose prescribed to HIV/AIDS patients in this section of the private health care sector of South Africa was therefore high. It is therefore recommended that more education be given to prescribers and dosage adjustments be done where indicated.

Key words: Drug-drug interactions, anti-retroviral drugs, prescribed daily doses, lopinavir/ritonavir, inappropriate prescribing, private health care sector, South Africa.

INTRODUCTION

The current guidelines for the use of anti-retrovirals (ARVs) do recommend the combinations of different ARV agents, due to the fact that these combinations have led to major improvements in the management of human

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immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in both developed and developing world (Arshad et al., 2009). ARVs have transformed the human immunodeficiency virus (HIV) infection from a fatal to a chronic illness due to their potency (Kiser et al., 2008). In spite of the so many beneficial effects of these ARVs, health care providers are faced with challenges of drug-drug interactions (DDIs) and drug-related adverse-effects (Tourret et al., 2007). Lopinavir/ritonavir (LPV/RTV) is a co-formulated boosted protease inhibitor (PI) containing lopinavir and low-dose ritonavir and forms part of the highly active antiretroviral therapy (HAART) for the treatment of HIV infection in adults and children (Oldfield and Plosker, 2006). As a PI, it is widely used for its high effectiveness in treating of both treatment-naive and -experienced HIV infected people (Chandwani and Shutter, 2008). Studies done on LPV/RTV recommended the standard twice daily dosage regimen, both in treatment-naive and -experienced children (Resino et al., 2004; Saez-Llorens et al., 2003). LPV/RTV is approved at a dose of 400 mg/100 mg every 12 h. While in treatment-naive patients the recommended dose is 800 mg/200 mg once daily, this regimen is not recommended for therapy in treatment-experienced patients (South African HIV Clinicians Society Clinical Guidelines, 2009). Its use in children below the age of 6 months, in terms of safety, efficacy and pharmacokinetics has not been established. Furthermore the once-daily dosing has not been evaluated, therefore the recommended dosage in children from 6 months to 12 months is 100 mg/25 mg to 400 mg/100 mg twice daily, and this is based upon the weight and body surface area of the child (Chandwani and Shutter, 2008). Drug-drug interactions (DDIs) involving PIs are common, for there are well known inhibitors of the 3A4 isoenzyme of cytochrome (CYP) P450 (Hughes et al., 2007). As with other PIs, lopinavir and ritonavir act as substrates for CYP 3A4 and CYP 3A5. Lopinavir is enzymatically inactivated by the cytocrome P450 3A4 isoenzyme; while ritonavir inhibits CYP 3A4 activity, resulting in the increase of plasma concentration of lopinavir and other substrates of CYP 3A4 (Cvetkovic and Goa, 2003). DDIs between LPV/RTV and other ARVs are complex, as has been demonstrated by the fact that LPV/RTV has the ability to induce its own metabolism, at the same time induce the metabolism of other drugs that are metabolized by CYP450 enzymes (Cvetkovic and Goa, 2003). For this reason LPV/RTV may have significant interactions with drugs that are inducers or inhibitors of these enzymes and more so with drugs that are substrates for the CYP3A4 and CYP3A5 (Chandwani and Shutter, 2008). One study determined the prevalence of possible DDIs between ARVs in different age groups and results reported a high prevalence of DDIs between ARVs that are inhibitors of CYP450 enzyme (Katende-Kyenda et al., 2008). The current study is relevant because LPV/RTV is an inhibitor of the CYP450 enzyme, thus presenting potential interac-tions with other ARVs metabolized by the same enzyme. Therefore the aim of this study was to determine potential DDIs between LPV/RTV and other ARVs in general practitioner's (GPs) and specialist's (SPs) prescriptions with inappropriate PDDs for years 2005 to 2007.

METHODOLOGY

This was a non-experimental, retrospective quantitative, drug utilization study performed on 49,995 (2005), 81,096 (2006) and 88,988 (2007) ARV prescriptions prescribed to HIV patients. Data were obtained from a South African Pharmacy Benefit Management (PBM) company managing the medical schemes medicines benefits of the private health care sector of South Africa. Data were selected for three years from 1 January, 2005 to 31 December, 2007. The following information was obtained from the database: drug's trade name, National Pharmaceutical Product Interface (NAPPI)-code, date of refilling the prescription, prescription number, number of medicine items prescribed, days supplied, patients' gender and age, treatment date (dispensing date). Unique encrypted, physician and pharmacy numbers (randomly allocated by the PBM) were used to avoid the identification of the patient, pharmacy and physician; thus maintaining anonymity. ARV drug names were classified according to pharmacological groups as described in the monthly index of medical specialities (MIMS) (Snyman, 2009). Prescribers of ARV prescriptions were divided into the following categories:

1. General practitioners (GPs): This group includes all the medical providers who are registered with the Health Professions Council of South Africa (HPCSA) as general medical practitioner.
2. Prescribers from the following specialist (SP) areas which include *inter alia:* Anaesthesiology, cardiology, paediatrics, clinical haematology, dermatology, gastroenterology, neurology, obstetrics and gynaecology.

Potential DDIs between LPV/RTV and other ARVs were identified and classified according to a clinical significant rating described in three degrees of severity: major, moderate and minor as described by Tatro (2003). Drug interactions assigned documentation levels of established, probable, or suspected were considered to be well substantiated and to have significance ratings of 1, 2 or 3 (Tatro, 2003). These interactions were considered to have a probability of occurring, while those ratings 4 or 5 were considered as not substantiated – having documentation levels of possible or unlikely. This study focused only on DDIs with clinical significance rating of 2 being the most common interactions between ARVs. According to Tatro (2003), clinical significance 2 can be considered to have a moderate severity, with effects causing deterioration in a patient's clinical status, thus requiring additional treatment, hospitalization or an extended hospital-stay. The study evaluated potential DDIs between LPV/RTV and other ARVs in GPs and SPs prescriptions with inappropriate PDDs for 2005 to 2007. According to World Health Organization (WHO), a PDD is defined as "the average dose prescribed according to a representative sample of prescriptions" (WHO, 2003). It is important that the PDD be related to the diagnosis made for the prescribed medication. The PDD of a drug can be calculated by multiplying the number of tablets (or volume of suspension or syrup) dispensed during the treatment period and the strength per tablet (or per ml), divided by the days supplied (WHO, 2003). In this study, the reference guides used to evaluate PDDs

were according to the recommended ARV- dosing guidelines (National Department of Health and Human Service, 2007). Basic descriptive statistics, that is frequencies, the arithmetic mean (average), standard deviations were used to characterize the study sample and were calculated using the computer software Statistical Analysis System® SAS for Windows 9.1® (SAS, 2006-2007). The age groups used in this study were: Group 1: 0 ≤ 12 years; Group 2: 12 ≤ 19 years; Group 3: 19 ≤ 45 years; Group 4: 45 ≤ 59 years and Group 5: > 59 years. For the purpose of this study a drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965, Act 101 of 1965 as amended as "substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man." In this research the words "drug items" are used interchangeably with the words "medicine items." In the South African context, a prescription can consist of one or more medicine items (or drugs). Permission to conduct the study was granted by the PBM Company and approval was obtained from the Research and Ethics Committees of the North-West University, Potchefstroom campus, (ethical number 07M01) and the Walter Sisulu University, Mthatha campus.

RESULTS

Of 2,638 GP and 472 SP ARV prescriptions claimed, 505 (19.1%) of GP prescriptions and 143 (30.3%) of SP prescriptions had DDIs and inappropriate PDDs as shown in Table 1. Of the total number of ARV prescriptions, potential DDIs were identified between LPV/RTV and other ARVs with incorrect PDDs accounting for 88.9% (n = 449) for GP and 98.6% (n = 141) for SP prescriptions. As observed in Table 1, the percentage of ARV prescriptions with potential DDIs increased from 2005 to 2006, remained almost the same from 2006 to 2007 for GP prescriptions while there was an increase from 2005 to 2007 for SP prescriptions. There was a percentage increase in the number of ARV prescriptions with potential DDIs and incorrect PDDs from 2005 to 2007 for both GPs and SPs. The same trend also reflected in the percentage of ARV prescriptions with potential DDIs between LPV/RTV and other ARVs with incorrect PDDs. In all these cases, there were more GP prescriptions as compared to SP prescriptions. The number of prescriptions with potential DDIs between LPV/RTV and other ARVs and with incorrect PDDs according to prescriber and age group is reflected per year in Tables 2 to 4. For the three years, the highest percentage of ARV prescriptions with potential DDIs and incorrect PDDs were with LPV/RTV at an average PDD of 1066.4 mg/264 mg and efavirenz (EFV) at an average PDD of 600 mg for both GPs and SPs prescriptions. Furthermore, these regimens were prescribed to patients in age group 19 to 45 years. In these regimens, GPs prescriptions were more, accounting for 61.5% (n = 276) and 38.3% of SPs prescriptions (n = 54). The total percentage of LPV/RTV prescriptions with potential DDIs and incorrect PDDs were for SP prescriptions accounting for 98.6% (n = 143) and 88.9% (n = 505) of GP prescriptions from 2005 to 2007 (Tables 2 to 4).

DISCUSSION

The aim of this study was to determine potential DDIs between LPV/RTV and other ARVs in GPs and SPs prescriptions with inappropriate PDDs. From the results obtained from this study, it was evident that the percentage of ARV prescriptions claimed from the PBM Company increased from 2005 to 2007. This may have resulted from an increase in the number of patients registered with medical schemes that claimed through the PBM. According to the WHO/UNAIDS press release, it was reported that in the Sub-Sahara Africa, the number of HIV-infected people who were receiving ART was steadily increasing as from year 2005 (WHO/UNAIDS, 2005), and of those, 5 million were living in South Africa (UNAIDS/WHO, 2007). It was also observed that LPV/RTV, the first co-formulated HIV-1 PI, was the most commonly prescribed and at the same time the PI with the most potential DDIs and with PDDs not according to the recommended ARV dosing. A review by Chandwani and Shutter reported that large clinical trials had demonstrated this drugs' efficacy in both treatment-naïve and experienced patients. Furthermore, the immunologic and virologic benefits of the same drug had been proven in HIV-infected adults, adolescents and children (Oldfield and Plosker, 2006).

DDIs were identified between LPV/RTV and EFV and nevirapine (NVP). As already stated LPV/RTV is a PI and EFV and NVP are non-nucleoside reverse transcriptase inhibitors (NNRTIs). According to studies performed by Seden et al. (2009), Clarke et al. (2008) and Miller et al. (2007), all PIs are predicted to have numerous DDIs because they are metabolized by the cytochrome P450 system and are also inhibitors of CYP3A4. Therefore it was not surprising that LPV/RTV interacted with EFV and NVP because non-nucleoside reverse transcriptase inhibitors (NNRTIs), like the PIs are also metabolized by the CYP450 and are also inhibitors of CYP3A4 (Malaty and Kuper, 1999). Potential DDI between LPV/RTV with EFV may result in increased or decreased concentrations of the PI. DDIs is a major concern to all health care providers especially those caring for HIV/AIDS, it is therefore recommended that multiple reminders and warnings be available whenever more than two medicines are administered. It was also evident that potential DDIs were identified between LPV/RTV at an average PDD of 800 mg/200 mg and EFV at an average PDD of 200 mg and NVP at an average PDD of 2600 mg, all prescribed to patients 12 years and younger. The safety, efficacy and pharmacokinetic profile of this drug have not been established in pediatric patients younger than 6 months

Table 1. Comparison of the number of ARV prescriptions with potential DDIs, ARV prescriptions with DDIs and inappropriate PDDs prescriptions with potential DDIs between LPV/RTV and ARVs with inappropriate PDDs according to type of prescriber and year.

Year	ARV prescriptions with potential DDIs (level 2)		ARV prescriptions with DDIs and PDDs not according to the recommended ARV dosing		ARV prescriptions with potential DDIs between LPV/RTV and other ARVs with PDDs not according to ARV dosing	
	GPs (%)	SPs (%)	GPs (%)	SPs (%)	GPs (%)	SPS (%)
2005	681 (25.8)	97 (20.6)	84 (16.6)	15 (10.5)	79 (17.6)	13 (9.2)
2006	976 (37.0)	179 (37.9)	183 (36.3)	63 (44.0)	168 (37.4)	63 (44.7)
2007	981 (37.2)	196 (41.5)	238 (47.1)	65 (45.5)	202 (45.0)	65 (46.1)
Total	2 638	472	505	143	449	141

Table 2. Number of LPV/RTV prescriptions with potential DDIs not prescribed according to recommended ARV dosing guidelines and age group for 2005

Age group (years)	Number of ARV prescriptions with DDIs (N = 84)	ARV combinations with average PDD			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
General practitioners					
0≤12	8	Lopinavir/Ritonavir	800/200	Efavirenz	200
	4	Lopinavir/Ritonavir	320/80	Nevirapine	2600
19≤45	30	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	1		4500/3999		1800
	15	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
	1		1066.4/264		500
45≤59	16	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	1	Lopinavir/Ritonavir	1066.4/264	Nevirapine	500
>59	3	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
Total	79				

Age group (years)	Number of ARV prescriptions with DDIs (N = 15)	ARV combinations with average PDD			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
Specialists					
19≤45	6	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	2		1142.6/282		600
	1		3999/990		1200
	2	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
	2		799.8/198		500
Total	13				

(De Maat et al., 2003). Because the analysis was done in age groups and not individual age of a specific patient and with the limitation that the weight of the patient was not available, it was difficult to compare the PDD with the recommended doses for a specific child. Nevertheless, the pediatric dosage prescribed in this study was high, considering that the recommended pediatric dose for LPV/RTV according to the treatment guidelines formulated by the National Department of Health South Africa in 2005 is < 15 kg + 12 mg LPV/kg and ≥ 15 kg =

Table 3. Number of LPV/RTV prescriptions with potential DDIs not prescribed according to recommended ARV dosing and age group for 2006.

Age group (years)	Number of ARV prescriptions with DDIs (N = 183)	ARV combinations with average PDD			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
General practitioners					
0≤12	6	Lopinavir/Ritonavir	800/200	Efavirenz	200
	3	Lopinavir/Ritonavir	320/80	Nevirapine	2600
19≤45	101	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	26		1066.4/264		400
	1	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
	2		799/198		1600
45≤59	11	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	7	Lopinavir/Ritonavir	1066.4/264		500
>59	9	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
	2	Lopinavir/Ritonavir	1066.4/264		500
Total	168				

Age group (years)	Number of ARV prescriptions with DDIs (N = 63)	ARV combinations with average PDD			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
Specialists					
19≤45	25	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	16	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
45≤59	22	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
Total	63				

10 mg LPV/kg twice daily. Therefore in this study, the PDD was high, considering that one capsule of LPV/RTV is 133.3 mg/33 mg, and the maximum dose should be 3 capsules (399.9 mg/99.9 mg) (National Department of Health South Africa, 2005). According to a study by Murphy et al. (2008), the recommended dosage for LPV/RTV in children is 100 mg/25 mg twice daily to 400 mg/100 mg, and this dose is based upon the body surface or the weight of the child. It is therefore recommended that ARV dosing for LPV/RTV be adhered to so as to avoid side effects like diarrhoea, nausea and vomiting, and metabolic derangements, including hyperlipidemia and glucose intolerance (Murphy et al., 2008). Results from this study also revealed that patients, 12 years and younger, were prescribed LPV/RTV and NVP at an average PDD of 2600 mg for years 2005 and 2006. This was a very high dose prescribed by GPs. According to the Department of Health Guidelines, the recommended pediatric dose for NVP is 10 mg/ml or 200 mg tablet as an initial dose and 4 mg/kg once daily for 14 days. Therefore this high dose could lead to adverse effects like rash including, Stevens-Johnson syndrome, symptomatic hepatitis, including hepatic necrosis (Murphy et al., 2008). In all three years, potential DDIs were identified between LPV/RTV at an average PDDs of 1066.4 /264, 4500/3999 and 1599.6 mg/264 mg to patients 19 to 45 years. As stated in the guidelines for the Department of Health and Human Service (2007), the standard dose for LPV/RTV in adults is 400 mg/100 mg (2 tablets or 5 ml) twice daily of LPV/RTV 800 mg/200 mg (4 tablets or 10ml) once daily. Therefore in this study the PDD for LPV/RTV was high and could lead to toxic levels with adverse effects like nausea, diarrhea and vomiting (Murphy et al., 2008). It is therefore recommended that the dose be adjusted to LPV/RTV 800 mg/200 mg (4 tablets or 10 ml once a day) for treatment-naïve patients. Though in this study it was not clear whether the dosage was for treatment-naïve or -experienced HIV patients, since information about these specific patients was not given. Nevertheless, the once daily dosing for LPV/RTV is only recommended for HIV-naïve patients, not for patients receiving EFV, NVP or NFV. According to the ART

Table 4. Number of ARV prescriptions with potential DDIs not prescribed according to recommended ARV dosing guidelines and age group for 2007.

Age group (years)	Number of ARV prescriptions with DDIs (N = 238)	ARV combinations with average PDD			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
General practitioners					
0≤12	9	Lopinavir/Ritonavir	640/160	Efavirenz	350
	6	Lopinavir/Ritonavir	799.8/198		200
19≤45	145	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	3	Lopinavir/Ritonavir	1599.6/264	Efavirenz	600
	8	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
	9	Lopinavir/Ritonavir	799.8/198		500
45≤59	17	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
>59	8	Lopinavir/Ritonavir	1066.4/264	Nevirapine	500
Total	202				

Age group (years)	Number of ARV prescriptions with DDIs (N = 65)	ARV combinations			
		ARV medicine item	PDD (mg/mg)	ARV medicine item	PDD (mg)
Specialists					
19≤45	23	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	16	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
45≤45	22	Lopinavir/Ritonavir	1066.4/264	Efavirenz	600
	3	Lopinavir/Ritonavir	1066.4/264	Nevirapine	400
>59	1	Lopinavir/Ritonavir	3999.9/990	Efavirenz	600
Total	65				

ART guidelines as per Department of Health and Human Sciences (2007) and National Department of Heath South Africa (2005), when LPV/RTV is given with EFV or NVP, the recommended dose for treatment-experienced patients is 600 mg/150 mg. Results from this study showed that LPV/RTV was the PI commonly prescribed by both GPs and SPs for three years. It was the drug with most potential DDIs with EFV and NVP and with incorrect PDDs. This could be due to prescribing-medication errors which could result in overdosing of LPV/RTV thus leading to serious adverse effects and furthermore leading to the non-achievement of the main treatment goals for ARV therapy in HIV/AIDS patients (Purdy, 2009). It is therefore recommended that dosage adjustments be made and more so, more education be provided to both GPs and SPs in the private health care sector in South Africa on LPV/RTV recommended dose and potential DDIs, with the aim of achieving an optimal therapy to the HIV/AIDS patients.

LIMITATIONS

Some limitations to this study were the non-availability of patient clinical data to do in-depth analysis of DDIs and PDDs analysis, as well as information on treatment-naive and -experienced HIV patients, and weights for the patients.

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