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Research Article

Genetic Alternations, Pharmacokinetics Variability and Drug Interactions of Unlicensed Drugs in Critically Ill Neonates and Infants

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ABSTRACT

Many studies were conducted to detect the magnitude of use of unlicensed drugs in neonates, infants and young children in many countries. No studies were conducted to detect the effect of genetic alternations, pharmacokinetics variability and drug interactions associated with the use of unlicensed medicationsin neonates and infants. This study aimed to detect the magnitude of use of these medications in patients admitted to the neonatal critical care unit and determine the proportion of drugs with specific pharmacokinetics variability and genetic alterations among the detected unlicensed drugs. The other objective was detecting the rates and categories of drug - drug interactions of the detected unlicensed medications. A prospective evaluation with descriptive analysis study design was used. The study was conducted on all the patients admitted to the neonatal and pediatric critical care units in a Maternity and children's hospital over twelve months' period. All drugs courses (prescriptions) administered to the preterm, neonates and infants were assessed to detect the incidence of the drug use. The main outcomes measured were the rates and categories of unlicensed medications used during hospitalization, the proportion of unlicensed drugs which may cause genetic alterations or inter individual variability and the incidence and nature of drug interactions occurred due to unlicensed drugs use. The patients received 1458 medication courses. Almost all (93%) of them administered at least one medication without license. The British National Formulary licensed use information were reviewed and a total of 460 unlicensed drugs were detected. The study concluded that pharmacokinetics variability in neonates and infants, genetic alterations and drug- drug interactions of the unlicensed drugs may significantly affect the efficacy and safety of treatments' regimens.

Keywords: Genetic alternations, pharmacokinetics variability, drug interactions, unlicensed drugs, neonates, infants

INTRODUCTION

Safety, efficacy, quality and positive benefit–risk balance are the main parameters determined by the clinical trials for any new drug before getting a license to be used in adults. Most of the clinical trials are performed in adults, as a result, many drugs were not tested or authorized for children's use. (1) Consequently, the use of unlicensed drug is very common in these patient population. (2) Thus, about 60% of children treated in hospital care settings prescribed at least one unlicensed drug (3) higher rates are reported in neonatal hospital care settings. (4-5) Calculating the correct dose for drugs in neonates and infants still remains an immense challenge. This is because

of lack of clinical trials in this population, the presence of many intrinsic factors such as genetics and inherited diseases and extrinsic factors such as diet, acquired diseases or other drugs may also affect the drug disposition. Children doses are often predicted by scaling from adult dosages after adjusting for body weight. Despite the major differences in the pharmacokinetic parameters between children and adults. Drug absorption, distribution, metabolism, and excretion are significantly different in children as compared with adults, and these processes change with aging when the child starts to grow and becomes more mature. (6) Pharmacokinetics processes are not mature in neonates and infants. Gastric pH and stomach emptying rate are different in neonates and infants than adults. This will affect the drug's absorption rate in this patient population. Drug's distribution also may be affected by the decrease in the serum protein concentrations and the increased amount of body water in this population. In neonatal period, the activity of the hepatic microsomal enzyme is decreased, but quickly enhanced over the first few months of life. Drug's elimination by the kidneys are low at birth, but develop over a few months. (7) Drug responsemay be affected by genetic factors, the presence of huge population differences with low intrapatient variability is consistent with inheritance as a determinant of drug response; about 20 to 95 % of variability in drug disposition and efficacy is resulted from genetic effects. (8) Medicationsefficacy may be affected by many nongenetic factors, including function of the organ, age of the patient, drug-drug interactions, concomitant therapy, and the nature of the disease, there are now many examples in which inter-individual variations in drug response are resulted from sequence variants in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets.(9-11)A drug–drug interaction is defined as increase or decrease in the clinical effect of a given drug due to interference by another drug (12) Drug drug interactions represent a main reason for mortality and morbidity worldwide (13) Drug interactions are one of the major challenges to the successful therapeutic outcomes(14). From all of the above, it is clear that prescribing a safe and effective drug during the first year of life presents unique challenges to the clinician, pharmacokineticist, and toxicologist. The objectives of this study were (i) Detect the extent of use of unlicensed drugs in critically ill neonates and infants < 1 year of age and the proportion of drugs with specific pharmacokinetics variability and genetic alterations among the detected unlicensed drugs. (ii) Detect the rates and types of drug drug interactions of the detected unlicensed drugs

MATERIALS AND METHODS

Design

Prospective evaluation with descriptive analysis study conducted on all the patients admitted to the neonatal intensive care unit and pediatric intensive care unit over twelve months' period.

Setting

Maternity and children's hospital

Subjects

Children aged 1 day to 1 year admitted to neonatal intensive care unit and pediatric intensive care unit were enrolled in this study. Patients were categorized to preterm (born before 37 weeks), neonate (birth to 1 month) and infant (1 month to 12 months)

Main outcomes measured

The proportion of drugs that were used in an unlicensed manner, the proportion of unlicensed drugs which may cause genetic alterations or inter individual variability and the incidence and nature of drug interactions occurred due to unlicensed drugs use.

Data collection and analysis

All drugs courses (prescriptions) administered to the preterm, neonates and infants were assessed to detect the incidence of the unlicensed drug use. Data of all patients admitted to the neonatal

intensive care unit and pediatric intensive care unit were collected by the clinical pharmacist (the main investigator) and assessed to determine if their use was unlicensed or not. The child's age, date of birth, weight, and diagnosis were recorded as well as details of all drugs administered (route of administration, dose, and indication for use). The licensed information was assessed based on the patients' ages. The primary reference sources for determining licensed information was the British National Formulary (BNF), 2017

Pharmacogenomics and pharmacokinetics information

A literature review was done to detect any correlation between the detected unlicensed prescribed drug and any inter individual differences in drug response due to sequence variants in genes. The rate was calculated by dividing the number of these drugs by the total number of the unlicensed drugs detected in all patients.

Drug_drug interactions detection

During the study, a systematic analysis of all aspects of patient treatment was performed in order to detect any drug _ drug interaction. The detected drug_ drug interactions were reviewed to detect if any unlicensed drug was involved in these interactions. If any unlicensed drug was involved in the drug _ drug interactions, the type and severity of this interaction were recorded. Drug _ drug interaction was recorded if one of the interacting drugs was unlicensed or if both of the interacting drugs were unlicensed. The proportion of the second type (both of the interacting drugs were unlicensed) was calculated by dividing the number by the total number of drug _ drug interactions. Medscape drug interaction checker was used to detect the drug_ drug interactions.

The study was approved from the ethical committee in the hospital.

RESULTS

A total of 245 preterm, neonates and infants were admitted to the neonatal intensive care and pediatric intensive care units during the study period of these, 159 (65%) of patients were male. The ages of the patients ranged from 1 day to 12 months. Patients' demographics are shown in

Table 1-Patients' demographics

Male	**Female**	**Neonatal ICU**	**Pediatric ICU**	**Preterm and neonates (< 1 month)**	**Infants (1 month – 12 months)**
No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
159 (65)	86 (35)	114 (47)	131 (53)	98 (40)	147 (60)

A total of 1458 drug courses (prescriptions) were administered to the patients. Patients received between 3 and 11 different drugs. Almost all (93%) of the patients administered at least one unlicensed drug. The British National Formulary licensed use information were reviewed and a total of 460 unlicensed drugs were detected. **[Table-2]** shows the detected unlicensed information of the 37 unlicensed drugs detected during the study period.

Table 2-The British National Formulary licensed use information of the detected drugs

	Drug	**BNF Licensed use information**	**N (%)**
1	Pipracillin	No license in children < 12 years (except for children 2–12 years with neutropenia and complicated intra-abdominal infections)	19 (5)
2	Atracurium	No license in neonates	4 (< 1)
3	Midazolam	No license in children < 6 months for premedication and conscious sedation	31 (7)
4	Paracetamol	No license in children < 2 months by mouth	24 (6)

5	Ranitidine	No license to be given orally in children < 3 years No license to be given parentally in children < 6 months	87 (19)
6	Meropenum	No license in children < 3 months	15 (3)
7	Imipenem/cilastatin	No license in children < 1 year or in children with renal impairment	15 (3)
8	Captopril	No license in children < 18 years	20 (5)
9	Aminophyllin IV	No license in children < 6 months	31 (7)
10	Ergocalciferol	No license in children <6 years	3 (< 1)
11	Flicanide	No license in children <12 years	3 (< 1)
12	Aspirin	No license in children <16 years	5 (1)
13	Salmeterol	No license in children <12 years	5 (1)
14	Omeprazole	No license to be given orally in children <1 years No license to be given parentally in children <12 years	19 (4)
15	Metolazone	No license in children	5 (1)
16	Propranolol	No license in children <12 years	4 (< 1)
17	Enoxaparin	No license in children	7 (1.5)
18	Vit D 3 Calcitriol	No license in children	14 (3)
19	Cotrimoxazole	No license in children < 6 weeks	3 (< 1)
20	Sildenafil	No license in children <1 year	13 (2.5)
21	Hydralazine	No license in children	15 (3)
22	Domperidone	No license in children for gastro-oesophageal reflux disease	33 (7)
23	Pyridoxine	No license in children	9 (2)
24	Ibuprofen	No license in children <3 months or body-weight < 5 kg	4 (< 1)
25	Dopamine	No license in children <12 years	10 (2.5)
26	Beclomethasone	No license in children <18 years	*21 (5)*
27	Acyclovir IV	No license in children < 18 years	9 (2)
28	Metoclopramide	No license in children	10 (2. 5)
29	Amiodarone	No license in children <3 years	4 (< 1)
30	Hydrochlorothiazide	No license in children	3 (< 1)
31	Levetiracetam	No license in children < 6 years or in children with body-weight < 25 kg, or for the administration of doses below 250 mg	*6 (1.3)*
32	Multivitamins	No license in children< 6 weeks	7 (1.5)
33	Lansoprazole	No license in children	3 (< 1)
34	Vit A	Preparations containing only vitamin A are not licensed	5 (1)
35	Chloral hydrate	No license in children	2 (< 1)
36	Cholestyramine	No license in children <6 years	3 (< 1)
37	Esmolol	No license in children	3 (< 1)
Total			460

Ranitidine was the most widely prescribed unlicensed drug, about 19 % of the detected unlicensed drugs. Midazolam, Aminophylline IV and Domperidone were the second most common detected unlicensed drugs (7%). Licensed information was correlated with the patients' ages, about 73 % (27 drugs) are not licensed for use in children without age specifications. Cotrimoxazole and multivitamins are not licensed for use in children under 6 weeks, paracetamol is not licensed for use in children under 2 months, Meropenem and Ibuprofen are not licensed for use in children under 3 months, Aminophylline IV, Midazolam and Ranitidine injection are not licensed for use in children under 6 months and Imipenem/cilastatin and Sildenafil are not licensed for use in children under 1 year.**[Figure -1]** shows the rates of unlicensed drugs detected during the study period. Genetic factors contribute to the high inter individual variability.

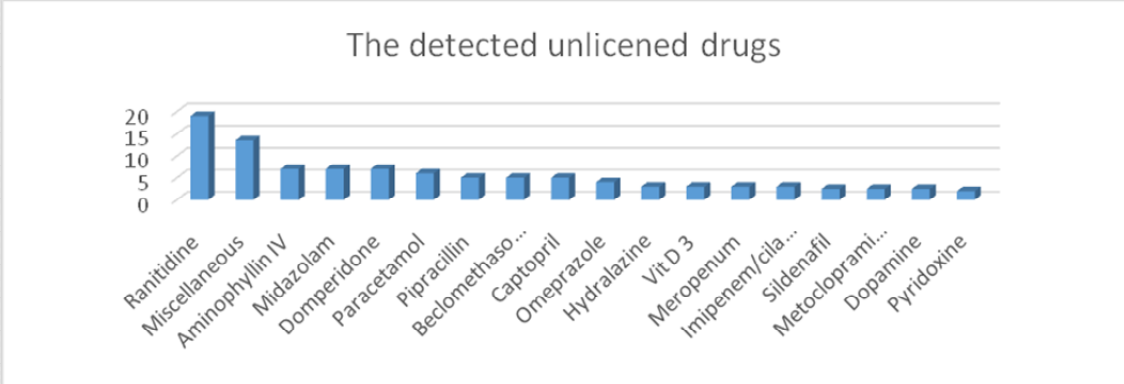

Figure 1-The detected unlicensed drugs

The genetics related information for the detected unlicensed drugs were reviewed and recorded as shown in **[Table-3]**

Table3 -Genetics related information for the detected unlicensed drugs

Drug	**Conclusion**	**Reference**
Ranitidine	low ranitidine N-oxidation was detected In Korean population because of FMO3/Lys158 and FMO3/Gly308 mutant alleles in FMO3 gene	(15)
Aminophyllin IV		NA
Midazolam	Its dosing was affected by SNPs in the candidate genes COMT, PXR and ABCB1 , but without any effect in the depth of analgosedation or withdrawal syndrome.	(16)
Domperidone	P-glycoprotein in the choroid plexus limits the accumulation of domperidone. Variable expression of P-glycoprotein in the duodenum was resulted from a single-nucleotide polymorphism; in patients homozygous for the T allele, duodenal expression of P-glycoprotein was less than half that in patients with the CC genotype.	(17) (18)
Paracetamol	The active metabolite AM404 molecule may involve a diverse range of pathways. These pathways are influenced by genetic variations which, with time, are likely to reveal a degree of inter-individual differences.	(19)
Pipracillin		NA
Esmolol/ Propranolol	Variations in genes may affect drug targets (e.g., receptors)	(20)
Captopril	Variations in genes may affect drug targets (e.g., receptors)	(21)
Beclomethasone	Polymorphisms in the SERPINA6 gene alter glucocorticoid binding and distribution, which may affect its toxicity. Overexpression and mutations in the glucocorticoid receptor gene (NR3C1) have	(22)

	been related to glucocorticoid resistance.	(23)
Calcitriol (Vit D 3)	The genetic variations in CYP24A1, VDR and GC genes may be associated with lower distribution of vitamin D	(24)
Omeprazole Lansoprazole	genetic variation in CYP-450 isoenzymes (CYP 2C19) results in altered effects proton pump inhibitors	(25)
Hydralazine	Genetic variants in the NAT2 gene may affect the acetylation status of the patients. 'fast acetylators' may have increased exposure to Hydralazine	(26)
Meropenum		NA
Imipenem/cilastatin		NA
Sildenafil	Genetic variations present in patients with hereditary degenerative retinal disorders.	(26)
Metoclopramide	Adults with NADH-cytochrome b5 reductase deficiency may developmethemoglobinemia and/or ulfhemoglobinemiaafter treatment Neonates have reduced levels of NADH-cytochrome b5 reductase and prolonged drug clearance, and therefore are also more susceptible to methemoglobinemia. NADH-cytochrome b5 reductase is encoded by the *CYB5R1*, *CYB5R2*, *CYB5R3* and *CYB5R4* genes.	(26)
Dopamine		NA
Pyridoxine		NA
Cotrimoxazole	*Prolonged QT interval is associated with KCNE2* variants sulfamethoxazolealso inhibits the potassium channels encoded by the *KCNE2* (8T→A) variant	(27)
Salmeterol	More than 13 distinct single-nucleotide polymorphisms have been identified in *ADRB2*. The bronchodilator response to inhaled β-agonist therapy revealed a stronger association between bronchodilator response and haplotype than between bronchodilator response and any single-nucleotide polymorphism alone.	(28)
Iburofen/ Aspirin	Variability in the genetic expression of the COX isoforms resulted in functional and clinical interindividual variability. Carriers of the COX-1 c.1676- >T (*rs1330344*) allele were found to have a significant risk of non-malignant gastric ulcers when using NSAIDs, while the COX-1 c.50C>T polymorphism was associated with an impaired inhibitory effect on aspirin, although it failed to demonstrate risk of peptic ulcer bleeding.	(29)
Acyclovir	Acyclovir has low but detectable influence on HLA-B*57:01 specificity without inducing hypersensitivity	(30)
Amiodarone	CYP2C8 activity may be affected by genetic polymorphism. The variant CYP2C8 P404A but not CYP2C8*3 has a lower intrinsic clearance for amiodarone N-deethylation compared with CYP2C8*1. Polymorphic alleles of CYP2C8 maylead to variations in the clinical response to amiodarone	(31)
Flecanide	CYP2D6 inhibition produced by flecainide among healthy volunteers	(32)
Metolazone		NA
Hydrochlorothiazide	Two polymorphisms in the sodium channel c-subunit promotor gene, and a polymorphism in the endothelial nitric oxide synthase gene, were linked to significant differences in odds of diastolic blood pressure response to the drug.	(33)
Levitracetam	Genetic factors contribute to the high interindividual variability in response to antiepileptic drugs.	(34)
Enoxaparin		NA
Chloral hydrate		NA
Cholestyramine		NA
Vitamin A		NA

Ergocalciferol		NA
Atracurium		NA
Multivitamins		NA

About 62% of the detected unlicensed drugs have evidence of genetic alterations which may result in inter individual variability to drugs responses. Many of the detected unlicensed drugs were involved in drug interactions with other drugs or other unlicensed drugs. A total of seventy two drug _ drug interactions were detected during the study period. Drug _ drug interactions severity and mechanisms are shown in **[Table-4].** The rate of the drug _ drug interactions that have been occurred between 2 unlicensed drugs was 34%.

Table 4 -The mechanisms and severity of the detected drug _ drug interactions due to the use of unlicensed drugs

The detected unlicensed drugs interactions	**Severity of the interaction**	**Mechanism**
*Amiodarone/Ranitidine	Use Caution/Monitor	Amiodarone will increase the level or effect of ranitidine by P-glycoprotein (MDR1) efflux transporter.
Ranitidine/ Cefuroxime	Use Caution/Monitor	Ranitidine will decrease the level or effect of cefuroxime by increasing gastric pH. Applies only to oral form of both agents.
Ranitidine/ Cyclosporine	Use Caution/Monitor	Ranitidine will increase the level or effect of cyclosporine by unknown mechanism.
Ranitidine/ ferrous sulfate	Use Caution/Monitor	Ranitidine will decrease the level or effect of ferrous sulfate (iron source) by increasing gastric pH. Applies only to oral form of both agents.
*Hydrochlorothiazide/ Ranitidine	Minor/Significance Unknown	Hydrochlorothiazide will increase the level or effect of ranitidine by basic (cationic) drug competition for renal tubular clearance.
Ranitidine/ Phenytoin	Minor/Significance Unknown	Ranitidine increases levels of phenytoin by decreasing metabolism.
*Sulfamethoxazole/ Ranitidine	Minor/Significance Unknown	Sulfamethoxazole will increase the level or effect of ranitidine by basic (cationic) drug competition for renal tubular clearance
Theophylline/ Carbamazepine	Serious, Avoid or Use Alternate Drug.	Carbamazepine will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Theophylline decreases levels of carbamazepine by increasing metabolism.
Erythromycin / Theophylline	Serious, Avoid or Use Alternate Drug.	Erythromycin base will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Cyclosporine /Theophylline	Use Caution/Monitor	Cyclosporine will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism..
Dexamethasone /Theophylline	Use Caution/Monitor	Dexamethasone will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
*Esmolol / Theophylline	Use Caution/Monitor	Beta blockers (esp. non selective) antagonize theophylline effects, while at the same time increasing theophylline levels and toxicity (mechanism: decreased theophylline metabolism).
Fluconazole / Theophylline	Use Caution/Monitor	Fluconazole will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Hydrocortisone / Theophylline	Use Caution/Monitor	Hydrocortisone will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Metronidazole / Theophylline	Use Caution/Monitor	Metronidazole will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Phenobarbital / Theophylline	Use Caution/Monitor	Phenobarbital will decrease the level or effect of theophylline by affecting hepatic enzyme CYP1A2 metabolism Phenobarbital will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Phenytoin / Theophylline	Use Caution/Monitor	Phenytoin will decrease the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Topiramate /	Use	Topiramate will decrease the level or effect of theophylline by affecting

Theophylline	Caution/Monitor	hepatic/intestinal enzyme CYP3A4 metabolism.
Midazolam / Amikacin	Use Caution/Monitor	Midazolam will decrease the level or effect of amikacin by P-glycoprotein (MDR1) efflux transporter.
Phenobarbital/ Midazolam	Use Caution/Monitor.	Phenobarbital will decrease the level or effect of midazolam by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Phenobarbital and midazolam both increase sedation.
Midazolam / Gentamicin	Use Caution/Monitor	Midazolam will decrease the level or effect of gentamicin by P-glycoprotein (MDR1) efflux transporter.
Ibuprofen / Gentamicin	Use Caution/Monitor	Ibuprofen increases and gentamicin decreases serum potassium. Effect of interaction is not clear.
Midazolam /Albuterol	Use Caution/Monitor.	Midazolam increases and albuterol decreases sedation. Effect of interaction is not clear.
*Ibuprofen/Captopril	Serious: Avoid or Use Alternate Drug.	Pharmacodynamic antagonism. Coadministration may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The mechanism of these interactions is likely related to the ability of NSAIDs to reduce the synthesis of vasodilating renal prostaglandins.
Ketamine /Midazolam	Use Caution/Monitor	Ketamine and midazolam both increase sedation.
Chlorpheniramine / Midazolam	Use Caution/Monitor	Chlorpheniramine and midazolam both increase sedation.
Midazolam / Pseudoephedrine	Use Caution/Monitor	Midazolam increases and pseudoephedrine decreases sedation. Effect of interaction is not clear, use caution.
Methylprednisolone / Midazolam	Use Caution/Monitor	Methylprednisolone will decrease the level or effect of midazolam by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Midazolam / Epinephrine	Use Caution/Monitor	Midazolam increases and epinephrine decreases sedation. Effect of interaction is not clear, use caution.
Erythromycin / Midazolam	Serious: Avoid or Use Alternate Drug.	Erythromycin base will increase the level or effect of midazolam by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Erythromycin base / Piperacillin	Use Caution/Monitor	Erythromycin base decreases effects of piperacillin by pharmacodynamic antagonism.. bacteriostatic agents may inhibit the effects of bactericidal agents.
Hydralazine / Epinephrine	Use Caution/Monitor	Pharmacodynamic antagonism. Sympathomimetics can antagonize the activity of some antihypertensive agents.
*Hydralazine /Dopamine	Use Caution/Monitor	Pharmacodynamic antagonism. Sympathomimetics can antagonize the activity of some antihypertensive agents.
*Midazolam / Dopamine	Use Caution/Monitor	Midazolam increases and dopamine decreases sedation. Effect of interaction is not clear
Epinephrine / Dopamine	Use Caution/Monitor	Epinephrine and dopamine both decrease sedation. epinephrine and dopamine both increase sympathetic (adrenergic) effects, including increased blood pressure and heart rate.
*Omeprazole / Midazolam	Minor/Significance Unknown	Omeprazole increases levels of midazolam by decreasing metabolism.
*Metoclopramide / Dopamine	Contraindicated	Metoclopramide decreases levels of dopamine by inhibition of GI absorption. Applies only to oral form of both agents.
Epinephrine / Metolazone	Use Caution/Monitor	Pharmacodynamic synergism epinephrine and metolazone both decrease serum potassium.
Vancomycin / Pyridoxine	Minor/Significance Unknown.	Vancomycin will decrease the level or effect of pyridoxine by altering intestinal flora. Applies only to oral form of both agents.
* Hydralazine / Pyridoxine	Minor/Significance Unknown.	Hydralazine decreases levels of pyridoxine by unspecified interaction mechanism.
Ceftazidime / Acyclovir	Minor/Significance Unknown.	Ceftazidime will increase the level or effect of acyclovir by acidic (anionic) drug competition for renal tubular clearance.
Acyclovir / Vancomycin	Minor/Significance Unknown.	Acyclovir and vancomycin both increase nephrotoxicity and/or ototoxicity.

*Metolazone / Acyclovir	Minor/Significance Unknown.	Metolazone will increase the level or effect of acyclovir by acidic (anionic) drug competition for renal tubular clearance.
Topiramate / Midazolam	Use Caution/Monitor	Topiramate will decrease the level or effect of midazolam by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Topiramate / Dopamine	Use caution. Modify Therapy/Monitor Closely.	Topiramate increases and dopamine decreases sedation. Effect of interaction is not clear
Carbamazepine / Paracetamol	Minor/Significance Unknown.	Carbamazepine decreases levels of Paracetamol by increasing metabolism.
*Enoxaparin / Ibuprofen	Modify Therapy/Monitor Closely	Enoxaparin and ibuprofen both increase anticoagulation.
Ibuprofen / Epinephrine	Use Caution/Monitor	Ibuprofen increases and epinephrine decreases serum potassium. Effect of interaction is not clear
* Esmolol / Ibuprofen	Use Caution/Monitor	Esmolol and ibuprofen both increase serum potassium. Ibuprofen decreases effects of esmolol by pharmacodynamic antagonism. Long term (>1 week) NSAID use. NSAIDs decrease prostaglandin synthesis.
* Ibuprofen / Hydralazine	Use Caution/Monitor	Ibuprofen decreases effects of hydralazine by pharmacodynamic antagonism. NSAIDs decrease prostaglandin synthesis.
Imipenem+ Cilastatin / Valproic acid	Serious: Avoid or Use Alternate Drug.	Imipenem/cilastatin decreases levels of valproic acid by unknown mechanism. Risk of seizure. Possible decreased GI absorption and/or increased renal clearance of valproic acid.
*Amiodarone / Trimethoprim+ Sulfamethoxazole	Serious: Avoid or Use Alternate Drug	Amiodarone and trimethoprim both increase QTc interval. Amiodarone and sulfamethoxazole both increase QTc interval.
Sulfamethoxazole / Cyclosporine	Serious: Avoid or Use Alternate Drug	Sulfamethoxazole decreases effects of cyclosporine by unknown mechanism. Increased nephrotoxicity with this combination.
*Sulfamethoxazole / Enoxaparin	Serious: Avoid or Use Alternate Drug	Sulfamethoxazole increases effects of enoxaparin by decreasing metabolism. sulfamethoxazole increases effects of enoxaparin by plasma protein binding competition.
* Trimethoprim /Captopril	Use Caution/Monitor	Trimethoprim and captopril both increase serum potassium. Trimethoprim decreases urinary potassium excretion. May cause hyperkalemia, particularly with high doses, renal insufficiency, or when combined with other drugs that cause hyperkalemia.
*Flecainide and Trimethoprim	Use Caution/Monitor	Flecainide and trimethoprim both increase QTc interval.
* Piperacillin / Enoxaparin	Serious: Avoid or Use Alternate Drug	Piperacillin increases effects of enoxaparin by anticoagulation. Piperacillin can inhibit platelet aggregation
Flecainide /Ondansetron	Serious: Avoid or Use Alternate Drug	Flecainide and ondansetron both increase QTc interval. Avoid with congenital long QT syndrome; ECG monitoring recommended with concomitant medications that prolong QT interval, electrolyte abnormalities, CHF, or bradyarrhythmias.
*Aspirin/Captopril	Serious: Avoid or Use Alternate Drug	Pharmacodynamic antagonism. Coadministration may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The mechanism of these interactions is likely related to the ability of NSAIDs to reduce the synthesis of vasodilating renal prostaglandins
*Amiodarone/ Captopril	Use Caution/Monitor	Either increases effects of the other by pharmacodynamic synergism. Both drugs lower blood pressure. Monitor blood pressure.
Phenobarbital/Captopril	Use Caution/Monitor	Phenobarbital, captopril. Either increases effects of the other by pharmacodynamic synergism. Both drugs lower blood pressure. Monitor blood pressure.
*Sildenafil/captopril	Use Caution/Monitor	Sildenafil, captopril. Either increases effects of the other by pharmacodynamic synergism. Both drugs lower blood pressure. Monitor blood pressure.
Captopril / Spironolactone	Use Caution/Monitor	Captopril, spironolactone. Either increases toxicity of the other by Mechanism: pharmacodynamic synergism. Both drugs lower blood pressure. Risk of

		hyperkalemia. Monitor blood pressure and potassium.
Carbamazepine/ Hydrochlorothiazide	Serious: Avoid or Use Alternate Drug	Carbamazepine, hydrochlorothiazide. Either increases effects of the other by pharmacodynamic synergism. Increased risk of systemic hyponatremia.
*Amiodarone / Hydrochlorothiazide	Use Caution/Monitor	Amiodarone will increase the level or effect of hydrochlorothiazide by basic (cationic) drug competition for renal tubular clearance
Levetiracetam / Pancuronium	Minor/Significance Unknown	Levetiracetam decreases effects of pancuronium by pharmacodynamic antagonism.
Carbamazepine / Omeprazole	Serious: Avoid or Use Alternate Drug	Carbamazepine will decrease the level or effect of omeprazole by affecting hepatic enzyme CYP2C19 metabolism.
*Metoclopramide / Dopamine	Contraindicated	Metoclopramide decreases levels of dopamine by inhibition of GI absorption. Applies only to oral form of both agents.
Clozapine / Dopamine	Contraindicated	Clozapine decreases effects of dopamine by pharmacodynamic antagonism.
Phenytoin/ Dopamine	Serious: Avoid or Use Alternate Drug	Phenytoin, dopamine. pharmacodynamic synergism. Increased risk of hypotension.
Acyclovir / Amikacin	Modify Therapy/Monitor Closely	Acyclovir and amikacin both increase nephrotoxicity and/or ototoxicity.

* Both of the interacting drugs are unlicensed

DISCUSSION

Children have the same right as adults to receive safe and effective drugs, many studies were conducted to detect the extent of use of unlicensed drugs in neonates, infants and children in many countries. This current study was the first study that focused on the genetic alterations and drug interactions of the detected unlicensed drugs. Pharmacokinetics variability in neonates and infants, genetic alterations and drug interactions may result in unexpected adverse effects with licensed drugs and these effects may have more dangerous consequences with unlicensed drugs. Pharmacokinetics variability in neonates and infants include variability in drug absorption, distribution, metabolism and excretion. The pH-dependent passive diffusion and gastric emptying are the two major factors that affect drugs absorption (35). These processes explain a variable but age related changes from birth till infancy and childhood (36).At birth, the gastric pH is about 6-8 and it is related to the presence of amniotic fluid in the stomach. Postnatally, the gastric acid secretory capacity appears after the first 24 to 48 hr of life and then decreases during the first weeks to months of life. Adult values are reached by 3 months of age. In premature infants, gastric pH may remain elevated due to immature acid secretion (37). This higher gastric pH may explain the higher serum concentrations of acid-labile drugs such as penicillins observed in neonates relative to older children and adults (38) Pipracillin is an extended spectrum penicillin prescribed for 19 neonates and infants during the study period, the BNF licensed use information search demonstrated that it is not licensed for use in children under 12 years of age. The presence of higher gastric PH in these neonates may lead to higher serum concentrations of pipracillin and neonates toxicity. Paracetamol was another unlicensed drug prescribed for 24 neonates as shown in table (2). Heimann G concluded that delayed absorption may occurs after paracetamol use in neonates (39). The distribution of drugs within the body. It is influenced by the amount and character of plasma proteins, and the relative volume of the fluid, fat, and tissue compartments of the body. Total body water is as much as 85% in preterm and 78% in full-term neonates. The

effect of an increased fraction of total body water is apparent when assessing the pharmacokinetic parameter-volume of distribution (V) - which relates drug concentration in plasma to the remaining portions of the body. Drugs which distribute in parallel with body water content like theophylline have higher V values for infants than adults (7). Aminophylline is a theophylline derivative prescribed with unlicensed use for 31 neonates and infants during this current study. The other factor that may affect theophylline pharmacokinetics is the enzymatic systems responsible for theophylline oxidation and methylation to caffeine. These systems are active in premature neonates; whereas, the development of enzymes for oxidative demethylation do not develop for several months of life (40). The capacity for drug metabolism by the neonatal liver is affected by the ontogeny of many drug-metabolizing enzymes. Rates of hepatic drug metabolism generally correspond with the expression of these enzymes, which is typically low at birth and gradually increases over time (41). Despite lower enzyme expression, reduced protein binding in neonates can sometimes lead to unexpectedly higher metabolic clearance of drugs (42). Table (2) shows the unlicensed drugs detected during this current study, many of these drugs are metabolized through CYP 450 isoenzymes; Midazolam (CYP 3A4), omeprazole, lansoprazol, amiodarone, sildenafil (CYP 3A4), Ibuprofen (CYP2C9), paracetamol (CYP2E1). Ibuprofen was prescribedin an unlicensed manner for 4 neonates in this current study. Skinner reported that ibuprofen has Low activity through 2–4 weeks of age; adult activity achieved by 1–6 months of age; activity exceeds adult levels by 3–10 y and returns to adult levels by puberty(43) and Hines reported that paracetamol's activity approximately 10% of adult activity in the newborn period; steadily increases to 30% by 3–12 months of age; reaches adult levels between 1–10 y of age (41). Midazolam and sildenafil have low expression at birth; increases to 30% adult levels by 1 month of age; almost fivefold increase by 3 months of age; full adult activity reached by 6 months of age; formulated infants may have faster maturation (44). Flavin-containing monooxygenase 1and 3 are involved in the metabolism of Ranitidine. Table (2) shows that ranitidine was prescribed for 87 patients, it was the highest prescribed unlicensed drug (19%) in this current study. Studies concluded that ranitidine has high serum levels during fetal period; suppression of expression can begin within days after birth; decrease in activity is not linked with increase in flavin containing monooxygenase 3; there may be a period with little flavin-containing monooxygenase activity (45). Drug clearance also may be variable in neonates and infants, Van Enk JG conducted a study to detect the pharmacokinetics of meropenem in preterm neonates and concluded that Meropenem has longer half-life in premature infants. Meropenem was prescribed in an unlicensed manner for 15 patients during this current study and this unexpected effect on the half-life may lead to unexpected accumulation and toxicity. The other factors that may affect drug responses are genetic alterations and drug interactions. Table (3) shows the genetics related information for the detected unlicensed drugs, 62% of the detected unlicensed drugs have evidence of genetic alterations to their responses which may result in unexpected adverse events especially in neonates and infants. In addition to the unique pharmacokinetics and pharmacogenomics variability of the detected unlicensed drugs, drug interactions was another factor which was studied during this current study. Table (4) shows the unlicensed drugs which were involved in drug _ drug interactions during the study period. A total of 72 drug_ drug interactions were detected, three of them were contraindicated and thirteen of them were classified as serious drug _ drug interactions which required discontinuation of one of the interacting drugs.

CONCLUSION

Use of unlicensed drugs to treat children is widespread. This problem is likely to affect children throughout the world, this is the first study that focused on this problem in Saudi Arabia. The most vulnerable pediatric group—critically ill neonates and infants—has the highest exposure to these unlicensed drugs. Pharmacokinetics variability in neonates and infants, genetic alterations and drug_ drug interactions of the unlicensed drugs may significantly affect the efficacy and safety of treatments' regimens. Serious adverse events may be associated with the use of these unlicensed drugs in critically ill neonates and infants; this situation underscores the need for clinical trials in these age groups. Clinical trials should take into consideration the highlighted factors (pharmacokinetics variability in this age group, genetic alterations and drug _ drug interactions of the unlicensed drugs) studied in this current study.

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