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BENEFICIAL EFFECT OF ESTABLISHING THERAPEUTIC DRUG MONITERING IN IRAQI HOSPITALS

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ABSTRACT

Background: The present research paper has been focused on the therapeutic drug monitoring (TDM) which refers to the individualization of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window). **The aim of the study** is to investigate the frequency of prescribing drugs that need monitoring to the patient admitted to the Iraqi hospitals at a single point of time or interval of time (for one month). **Methodology:** A cross-sectional study for the prescribing drugs which are known to be commonly needed monitoring using the patients' case sheet in all over departments of many Iraqi hospitals for one month recruiting 120 patients were treated with drugs known to be monitored. **Results**: the most risky groups are represented by the elderly and neonates (32.5% and 34.17% respectively) that is because the neonates and infants have increased total body water to body fat ratio compared to adults, whereas the reversed is observed in elderly people. **Conclusion:** it is mandatory to establish a therapeutic drug monitoring service at the Iraqi hospital which at least serves the hospital inpatients so leading to improve the quality of patient care, reduce drug related toxicity, and also minimize liability of physician

KEYWORDS: TDM, Pharmacokinetic, pharmacodynamics, steady state, digoxin.

INTRODUCTION

Overview

Therapeutic drug monitoring (TDM) refers to the individualization of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window).[1] TDM has been routinely practiced in clinical laboratories since the mid–1970s, but the scientific foundations of the subject date back to the 1940s, when Marshall first tested the concept that the activity of a drug is dependent on its plasma concentration. [2] The science of Therapeutic Drug Monitoring grew out of the recognition that certain drugs have a narrow therapeutic range, in concentrations above the upper limit of the range, the drug can be toxic, in concentrations below the lower limit of the range, the drug can be ineffective and finally not all patients have the same response at similar doses.[3] However therapeutic drug measuring is only one part of therapeutic drug monitoring (TDM) which provides expert clinical interpretation as well as the concentration. There is rarely financial provision for this. Nevertheless expert interpretation of a drug concentration measurement is essential to ensure full clinical benefit. Only clinically meaningful tests should be performed and limited funds should not be wasted on measurements which cannot be interpreted and do not assist patient management.[4]

When an effect, such as changes in blood pressure, pain or serum cholesterol is readily measured, the dose of a drug should be adjusted according to the response. Monitoring drug concentration is more useful when drugs are used to prevent an adverse outcome and the drug should satisfy certain criteria to be suitable for therapeutic drug monitoring like in, narrow target range, significant pharmacokinetic variability, a reasonable relationship between plasma concentrations and clinical effects, established target concentration range and availability of cost-effective drug assay.[5]

Factors that affect results

Many factors contribute to the production of an accurate and meaningful drug level measurement:

- Pharmacokinetics
- Pharmacodynamics
- Dose
- Sampling time and type
- Testing methodology
- Genetic polymorphisms. [6]

But the two major sources of ***variability*** between individual patients in drug response are:

1- Dose and plasma concentration (*pharmacokinetic variability*)
2- Drug concentration at the receptor and the response (*pharmacodynamic variability*). Pharmacodynamic variability describes the way in which the drug affects the body's functions, and the relationship between the drug's chemical structure, actions, and effects.*(see fig.1)*

Pharmacokinetic variability pharmacodynamic variability

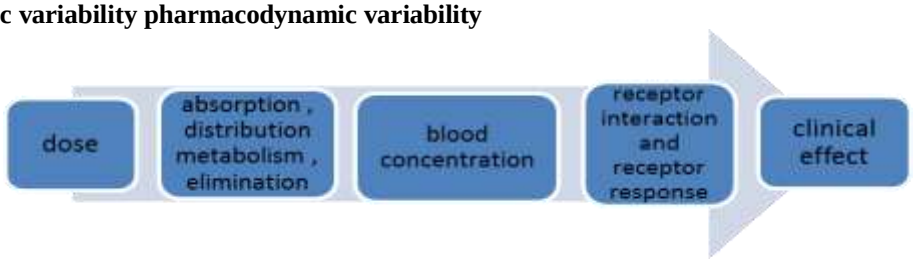

Fig. 1: Pharmacokinetics and pharmacodynamics contribute to variability in the relationship between drug dose and response.[1]

The major sources of pharmacokinetic variability are the patient compliance (lack of), age (neonates, children, elderly), physiology (gender, pregnancy), disease (hepatic, renal, cardiovascular, and respiratory), and drug-to-drug interactions.[6]

Factors that Affect Interpretation: The sample information required for accurate interpretation is the followings:

- Time of sample in relation to last dose
- Duration of treatment with the current dose
- Dosing schedule
- Age, gender
- Other drug therapy
- Relevant disease states
- Reason for request (e.g. lack of effect, routine monitoring, suspected toxicity).[6]

Steady State

Steady state is defined as the point at which drug intake and elimination reach equilibrium, and the height of the peak and the depth of the trough are predictable. Steady state is reached after 5-6 half lives of the drug. The goal of therapeutic drug monitoring is to optimize the drug dose so the patient's drug concentrations remain within the therapeutic range for the drug.[6]

Commonly Monitored Drugs

There are several classes of drugs commonly monitored to ensure correct blood concentration, including the following:

- Antiepileptics (Carbamazepine, Phenobarbital, Phenytoin, Valproic acid)
- Antiarrythmics (Digoxin, Lidocaine)
- Antibiotics (Gentamycin, Amikacin, Vancomycin)
- Antineoplastics (Methotrexate)
- Antimanics (Lithium)
- Bronchodilators (Theophylline)
- Immunosuppressives (Cyclosporine, Tacrolimus).[7]

THE AIM OF THE STUDY

Is to investigate the frequency of prescribing drugs that need monitoring to the patient admitted to the Iraqi hospitals at a single point of time or interval of time (for one month) and rationalize the urgency of measuring drug concentration and establishing a therapeutic drug monitoring service in our hospital to optimize patient s clinical outcome.

METHODOLOGY

A cross-sectional study for the prescribing drugs which are known to be commonly needed monitoring using the patients' case sheet in all over departments of many Iraqi hospitals for one month.

Then each prescription was studied according to the major pharmacokinetic variability of the patient (age, gender, disease status and drug-drug interaction), so the urgency of measuring drug concentration and drug monitoring have been detected and estimated for each drug according to the patient medical history and his/her pharmacokinetic variability as well as duration of therapy that is recorded in the patient's file.

After that the data was statistically estimated using the probability value that evaluates which cases are significant (need to be monitored) or not.

RESULTS AND DISCUSSION

From 4470 admitted patients for one month in all over departments of Iraqi hospitals, there are 120 patients was treated with drugs known to be monitored and according to their demographic data that are shown in table 1 the most risky groups are represented by the elderly and neonates (32.5% and 34.17% respectively) that is because the neonates and infants have increased total body water to body fat ratio compared to adults, where as the reversed is observed in elderly people. These factors may affect the volume distribution of drugs depending on their lipophilic character. Moreover, altered plasma

binding of drugs may be observed in both neonates and some elderly people due to low albumin, thus increasing the fraction of pharmacologically active free drug. In general, the drug metabolizing capacity of liver enzyme is reduced in new born and particularly in premature babies. Also renal function at the time of birth is reduced by more than 50% compared with adults but then increased rapidly in the first 2-3 years of life.[8]

The gender factor also is investigated in this table for adults only where the females 42(35%) are more than males 37(30.83%). The gender difference affects bioavailability, distribution, metabolism and elimination of drugs due to variation between men and women in body weight, blood volume, gastric empting time, drug protein binding activities of drug metabolizing enzymes, drug transporter function and excretion activity. In general the average male has higher body weight, greater body surface area and total water content compared to the average female causes differences in volumes of distribution of certain drugs.[8]

Table 1: Demographic data of patients[#][n=120].

Parameters	N (%)
Age groups	
>=60 years (elderly)	39(32.5%)
<60	40(33.33%)
Neonates	41(34.17%)
Gender (except neonates)	
Male	37(30.83%)
Female	42(35%)

Patients [#] represents the hospital's inpatients taking the drugs known to be monitored for one month

Table 2 shows the frequency of prescribing drugs known to be monitored in all over cases that was founded in our hospital (147 prescriptions) which from in-betweens Gentamycin was the most prescribed drug and the Phenobarbital was the less one.

Table 2: Frequencies of prescribing drugs known to be monitored to the patients [N*=147].

Prescribed Drug	N (%)
Digoxin	24(16.33%)
Aminophylline(Theophylline)	28(19.04%)
Carbamazepine	22(14.96%)
Phenobarbital	3(2.05%)
Gentamycin	45(30.62%)
Amikacin	12(8.16%)
Vancomycin	13(8.84%)

N*represents the sum of prescribed drugs known to be monitored during one month

When each drug was studied individually (Table 3), each pharmacokinetic parameter that affects the interpretation of drug concentration was appreciated.

Table 3: Pharmacokinetic parameters for each drug.

Drug	Age	Patients' Disease Status	Drug –Drug Interactions	Omitted cases
Digoxin (n=24)	Elderly 20(83.33%)	Renal 15(62.5%) Hepatic 3(12.5%) Cardiovascular 24(100%) Electrolyte imbalance (decreased K^+ level) 4(16.6%)	24(100%) 22 with Furosemide 7 with Amiodaron and 15 with Atrovastatin	0
Theophylline (Aminophylline) (n=17)	Elderly 7(41.17%) Neonate 1(5.9%)	Hepatic 1(5.9%) Cardiovascular 2(11.76%) Electrolyte imbalance (decreased K^+ level) 1(5.9%) Hyperthyroidism 1(5.9%)	2(11.76%) with Phenobarbital and Carbamazepine	3(17.64%)
Carbamazepine (n=22)	Elderly 10(45.45%)	Hepatic 1(4.45%) Cardiac 9(40.9%) Renal 6(27.27%)	3(13.63%) with INH Clarithromycin and Aminophylline	13(59.09%)
Phenobarbital (n=3)	Neonate 1(3.33%)	Respiratory 1(3.33%)	1(3.33%) with Aminophylline	2(66.66%)
Gentamycin (n=45)	Elderly 4(8.88%) Neonate 28(62.22%) Female 9(20%)	Renal 3(6.66%)	4(8.88%) with Frusemide and Vancomycin	0
Amikacin (n=12)	Neonate 10(83.33%) Female 2(16.66%)	Renal 1(8.33%) Burns 1(8.33%)	8(66.66%) 1 with Vancomycin 8 with cephalosporins	0
Vancomycin (n=13)	Elderly 4(30.76%) Neonate 5(38.46%)	Renal 2(15.38%)	3(23.07%) with aminoglycosides	0

n=no. of prescribed drugs individually during one month

Digoxin

Digoxin has a narrow therapeutic Index and the elderly patient (83.33% of cases) may be particularly susceptible to digoxin toxicity, even at therapeutic plasma concentrations.[9]

A number of factors may influence the response to digoxin and thus the interpretation of digoxin assays, when it is increased in renal failure and hepatic disease and by concurrent use with amiodarone and possibly atrovastatin. The electrolyte imbalance (decreased k^+, and /or Mg^{2+} or raised Ca^{2+}) can potentiate toxicity. [10] Since digoxin is a major substrate for P- glycoprotein and amiodarone is a known inhibitor of P-glycoprotein, the primary mechanism by which amiodarone increases digoxin concentrations is through its ability to inhibit the efflux of digoxin (gastrointestinal elimination and renal tubular secretion) from the body. Another mechanism that may also be contributing to the changes in serum concentrations is a redistribution of digoxin from tissue to serum. This appears to be based on the concentrations of amiodarone present; as amiodarone concentrations increase so do serum digoxin concentrations. This change in tissue distribution can affect the interpretation of serum digoxin levels.[11]

Drugs that cause electrolyte disturbances increase the risk of toxicity from cardiac glycosides. Thiazides and loop *diuretics* cause hypokalaemia and also hypomagnesaemia which may lead to cardiac arrhythmias.[9] Atorvastatin co administration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion.[12]

Aminophylline (Theophylline)

Theophylline or aminophylline should be given with caution to patients with peptic ulceration, porphyria, hyperthyroidism (5.9%), hypertension, cardiac arrhythmias or other cardiovascular disease (11.76%), or epilepsy, as these conditions may be exacerbated. They should also be given with caution to patients with heart failure, hepatic dysfunction (5.9%), acute febrile illness, and to neonates and the elderly(5.9% and 41.17% respectively in our study), since in all of these circumstances theophylline clearance may be decreased, resulting in increases in serum-theophylline concentrations and serum half-life.

Although *phenobarbital* was not found to have a significant effect on the pharmacokinetics of a single dose of theophylline given intravenously, enhanced theophylline clearance has been seen in patients after longer periods of treatment with phenobarbital. *Carbamazepine* has also been seen to increase theophylline elimination. [9] Tow cases of interaction was found in our study one with phanodarbital and the other for carbamazepine.

Carbamazepine

Carbamazepine clearance is decreased in an age-dependent manner in elderly patients (45.45%) compared with younger subjects, presumably because a reduction in the rate of CYP3A4-mediated drug metabolism.[13] Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac (40.9%), hepatic (4.45%), or renal disease (27.27%). Clinical monitoring is of primary importance throughout treatment.

A decrease in serum-carbamazepine concentrations of about 50% was reported in an epileptic patient given theophylline. The patient experienced seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine. The antimycobacterial *isoniazid* and macrolides such as *clarithromycin*, and *erythromycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity.[9]

Phenobarbital

Monitoring of plasma concentrations has been performed as an aid in assessing control. The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. There is considerable inter individual variation in Phenobarbital kinetics.[9]

The same interaction of Phenobarbital with aminophylline is mentioned above.

Aminoglycosides (gentamycin and amikacin)

The risk of ototoxicity and nephrotoxicity from aminoglycosides is increased at high plasma concentrations and it is therefore generally desirable to determine dosage requirements by individual monitoring. Monitoring is particularly important in patients receiving high doses or prolonged courses, in infants (62.22% for gentamycin, 83.33% for amikacin) and the elderly (8.88% for gentamycin), and in patients with renal impairment (6.66%% for gentamycin, 8.33%% for amikacin), who generally require reduced doses. Female sex has been reported as additional risk factors for nephrotoxicity. The *BNF* also considers monitoring to be important in patients with cystic fibrosis or significant obesity; again, altered doses may be required.[9]

Plasma concentrations may be reduced in patients with conditions which expand extracellular fluid volume or increase renal clearance including ascites, cirrhosis, heart failure, malnutrition, spinal cord injury, burns (8.33%% for amikacin), cystic fibrosis, and possibly leukaemia.

Use of other nephrotoxic drugs (including other aminoglycosides, vancomycin, and some cephalosporins), or of potentially ototoxic drugs such as furosemide, may increase the risk of aminoglycoside toxicity.[9]

The aminoglycoside interacts with the cell membranes in the inner ear, increasing their permeability. This theoretically allows the loop diuretic to penetrate into the cells in higher concentrations, causing more severe damage.[14]

Vancomycin

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment (15.35% of cases), in neonates (38.46% of cases) (especially if premature), and in the elderly (30.76% of cases), all of whom may be at increased risk of toxicity.

Again other ototoxic or nephrotoxic drugs, such as aminoglycosides and loop diuretics, markedly increase the risk of toxicity and should be given with vancomycin only with great caution.[9]

Steady state concentration consideration

The last column in Table 3 mention the omitted cases which based on the all pharmacokinetic parameter described above in relation to the steady state concentration for each drug.

So for digoxin, gentamycin, amikacin and vancomycin all cases need measuring the plasma concentrations without reaching steady state concentrations and each patient need to individualize his dose according to the other presented risk factors.

For theophylline, carbamazepine and Phenobarbital where (17.64%, 59.09% and 66.66% omitted cases respectively) because they do not reach their steady state concentrations as well as their lower risk factors that recommended to measure the plasma drug concentration.

P-value

In Table 4 our data were statistically estimated using probability table and all values were significant (need monitoring) except carbamazepine and Phenobarbital as they have more than 0.05 P-value.

Table 4: Probability.

Drug	No. of cases need monitoring	No. of cases not need monitoring	P value
Digoxin (n=24)	24	0	0.000
Theophyllin (Aminophyllin) (n=17)	14	3	0.007
Carbamazepine (n=22)	9	13	0.393
Phenobarbital (n=3)	1	2	0.317
Gentamycin (n=45)	45	0	0.000
Amikacin (n=12)	12	0	0.0005
Vancomycin (n=13)	13	0	0.0003

n=no. of prescribed drugs individually during one month
0.0 = less than 0.0001

CONCLUSION AND RECOMMENDATIONS

According to the results and widely prescribed drugs needed monitoring in our hospital, the study is to be concluded that it is mandatory to establish a therapeutic drug monitoring service at the Iraqi hospital which at least serves the hospital inpatients so leading to improve the quality of patient care, reduce drug related toxicity, and also minimize liability of physician. It is recommended that ministry of health must increase the number of highly trained staff specialized in therapeutic drug monitoring and drug analysis.

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