Caution from using cardiac glycosides digoxin drug which have properties therapeutic index (Ti) narrow compare with the medications wide therapeutic index
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Abstract
Clinical research will be based on the practical application of randomly assigned patients over the age of 25 who numbered 730 at the Academic Teaching Hospital in Iraq - Samawa. We used drugs narrow therapeutic index (NTI), which is used with caution at a specific and calculated dose because it is life-threatening and has high toxicity. Compared to drugs that have wide therapeutic index (WTI) and less serious effects (such as aspirin, acetaminophen (paracetamol), penicillin, etc.), we selected acetaminophen (paracetamol) in patient research (a wide therapeutic index) and the dose and ratio between the toxic dose and the safe therapeutic dose of the drug, the research focuses on dilution To limit the risk of medication to patients (mortality), which is used as a measure of the relative safety of the drug in a particular drug treatment, our main work is limited to digoxin (cardiac glycosides) used in heart disease, discrimination with other drugs and knowledge, and in comparison to drugs. We used acetaminophen (paracetamol) which is a broad indicator, so we based on previous knowledge in clinical pharmacy, dosage medications, therapeutic toxic dose, maximum dose, initial dose, maintenance dose, lethal dose, by knowing Therapeutic index for drug identification, therapeutic index, therapeutic ratio, TI can be calculated as a lethal dose of the drug by 50% of the population (LD50) divided by the minimum effective dose for 50% of the population (ED50), that is, TI = LD50 / ED50. This "academic" definition of TI is easier to follow in preclinical trials but opens the door to changing explanations in clinical practice. In fact, the definition of therapeutic and / or toxic effect in humans is highly dependent on the type of therapeutic or toxic effect under study, and the drug is generally considered to have a good safety appearance if its TI values exceed the value of 10. The situation is quite different from so-called narrow TI drugs (NTIDs) . Where only a very small set of doses produce a beneficial effect without causing severe and fatal complications, i.e. small differences in their plasma concentrations can lead to inadequate therapeutic response or the appearance of harmful toxic effects.

The term “critical dose medication” is sometimes used to refer to drugs where relatively small differences in dosage or concentration may lead to serious therapeutic failure and / or serious drug reactions. Other terms used also include "narrow therapeutic window drugs", "narrow therapeutic range", "critical anti-dose drugs" or "narrow therapeutic ratio . According to: The US Food and Drug Administration (FDA) defines a medication product as containing NTI when (a) there is less than a double difference in LD50 and medium effective dose values (ED50) or (b) there is less than a double difference in toxic concentrations Minimum (MTC) and minimum effective concentrations (MEC) in the blood and (c) safe and effective use of the drug requires careful calibration and patient monitoring 2018.

Keywords: cardiac glycosides digoxin drug, therapeutic index (Ti), medications

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Introduction
Clinical scientific research has been focused on the use of narrow digoxin drugs with narrow therapeutic index (NTI),[15] which are used with caution at a specific and calculated dose because they are human life-threatening and have toxicity for example[16] We defined the following drugs to be NTI-drugs[12-21] (digoxin, carbamazepine, aminoglycosides, digitoxin, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline and warfarin.) Among drugs that have a wide therapeutic index (WTI) , which are used in large doses and more and the toxic effect is far and less serious example WTI-drugs[17] (Aspirin . Acetaminophen (paracetol), penicillin, Beta-blokers, most antibiotics), ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment. Our main work is limited to digoxin (cardiac glycosides) used in heart disease and discrimination with other drugs and knowledge, and compared with drugs and we used a substance that is
safer Acetaminophen (paracetol) so we based on the prior knowledge of clinical pharmacology. Dose drug, therapeutic dose, maximum tolerated dose. Initial dose, maintenance dose, lethal dose (fatal dose), by knowing therapeutic index of the drug definition\(^{10,18}\) (Therapeutic Index (TI) = Measure of drug safety is the ratio of the dose that produces toxicity in half the population (TD\(_{50}\)) to the dose that produces a clinically desired or effective response (ED\(_{50}\)) in half the population). Therapeutic index:

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 TI = \frac{LD_{50}}{ED_{50}}
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In search used Digoxin "- (Narrow therapeutic index)\(^{13,14}\). The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis\(^{6,7}\) (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are widely used in treating HF\(^{4,8,9}\). Like the antiarrhythmic\(^{11,15}\) Caution must be exercised when using this medication as it has many drug interactions which can further increase the likelihood of adverse events. Digoxin, a cardiac glycoside, exerts its positive inotropic effects by inhibiting the plasma membrane Na\(^+\), K\(^+\)-ATPase of cardiac myocytes. This leads to an increase in available Ca\(^{2+}\) as described above. While digoxin has been in clinical use for hundreds of years as an inotrope and to control heart rate in atrial fibrillation, it has largely been replaced by more effective medications with fewer side effects. Cardiac glycoside that is useful for rate control in patients with atrial fibrillation and as a supplementary treatment for heart failure. At therapeutic doses, digoxin has a parasympathomimetic Digoxin is currently indicated (as a second or third line therapy) for ventricular rate control in atrial fibrillation and in the treatment of systolic heart failure. concentration monitoring, and its use is frequently associated with a wide variety of cardiac arrhythmia including sinus bradycardia, sinus arrest, AV conduction delays, second- or third-degree heart block, and malignant ventricular arrhythmias. Digitalis toxicity is generally treated with digitalis binding antibody as well as lidocaine, magnesium, phenytoin, and correction of hypokalemia. There is relative contraindication for the use of digoxin in the presence of atrioventricular block, sinus bradycardia, ventricular tachycardia, Wolff-Parkinson-White syndrome, hypokalemia, hypercalcaemia, hypomagnesemia, or renal insufficiency and should be used with caution in hypertrophic cardiomyopathy due to the known association with accessory pathways. Cardiac toxicity is exacerbated by hypokalemia, hypercalcaemia, and hypomagnesemia. Cardiac toxicity is exacerbated by hypokalemia, hypercalcaemia, and hypomagnesemia. Noncardiac signs of toxicity include nausea, vomiting, diarrhea, delirium, agitation, and visual disturbances. Absorption of oral digoxin from the gastrointestinal tract is variable from one individual to another and dependent upon the formulation. The onset of action after an oral dose occurs within 30 to 120 minutes and peaks at approximately 6 to 8 hours. The effects of IV digoxin begin after 5 to 30 minutes. The elimination half-life in adult patients with normal renal function is between 36 and 48 hours and prolonged in renal dysfunction. The second drug Acetaminophen it used in the research that therapeutic index wide Major use Acetaminophen is analgesic and anti-pyretic drug, with some anti-inflammatory activity. Inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity. Acetaminophen does not affect platelet function or increase blood clotting time. Initial adverse effects of poisoning may be non-specific (nausea or vomiting) or absent. Therapeutic dose in adults is 1-4 g/day. The minimum lethal dose in adults is 5-15 g; the acute lethal dose ranges from 13 to 25 g
, in the plasma half-following an overdose, the peak plasma level is not usually reached for 4 hours, and sometimes it may exceed 12 h, indicating very likely a hepatic coma.

Materials and methods

Our work on patients was applied in the study Collage of medicine and at Al-Samawa General Hospital and Diabetes and Endocrinology Center since January 2019. Work within the hospital and outpatient clinics and collection of patients and patient history, and the calculation of dosage, and the safe dose, toxic doses and poisoning to patients with taking all necessary precautions to save the patient and take the medicine correctly and honestly. 730 patients were randomized to 25≤ years (adult) and the doses of digoxin I group: were 190 patients using NIT oral medication maintenance dose is 0.125 to 0.25 mg daily A typical adult loading-dose regime involves 500 μg one dilly or then two doses of 250 μg two daily. Digoxin has an oral bioavailability of 75%. If rapid heart-rate control is required the loading dose should be given intravenously. Digoxin is excreted largely unchanged by the kidneys, and the maintenance dose should be reduced in patients with renal impairment. The therapeutic range is 0.6 to 2 nmol/l (or 0.5 to 1.5 ng/ml), and toxicity occurs with levels above 2.6 nmol/l (2 ng/ml). The onset of action after an oral dose occurs within 30 to 120 minutes and peaks at approximately 6 to 8 hours. The effects of IV digoxin begin after 5 to 30 minutes. The elimination half-life in adult patients with normal renal function is between 36 and 48 hours and prolonged in renal dysfunction. With caution only for emergency cases we were given intravenously inside the hospital. The optimal dosage when giving the patient by mouth is working rest period of medication (Stop the medication day during the week).

The 2 group: Acetaminophen (paracetamol) We have used the drug on many patients on a larger scale because therapeutic index wide. More freely 540 patient therapeutic dose in adults is 1-4 g/day. The minimum lethal dose in adults is 5-15 g; the acute lethal dose ranges from 13 to 25 g. We used 1500 mg daily safely on the patient’s condition to not complain of stomach problems or ulcers were normal things. Therapeutic blood (its serum or plasma) concentrations range from 5 to 20 mg/l. Toxic blood concentrations are in the range of 25-150 mg/l. The elimination of metabolized drug is via kidney. Metabolism and excretion. About 90% of acetaminophen is biotransformed by cytochrome P-450 in the liver. So we worked comparing Of the 730 patients included, 190 patients (33%) used NTI-drugs, The NTI-drugs were significantly more often associated with DRPs (drug related problem) than the non-NTI-drugs. The drug risk ratio was 0.50 for NTI-drugs and 0.20 for non-NTI-drugs. Use optimal dose.

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
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<tr>
<td>Digoxin curve</td>
<td>paracetamol curve</td>
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<td>Narrow TI</td>
<td>Wide</td>
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**Electrocardiographic change**

At nontoxic doses, digoxin does not exert obvious effects on the sinus rate, PR interval, QRS duration, or QT interval. Patients treated with digoxin often develop downsloping of the ST segment, which is known as “digoxin effect.” At toxic doses, patients can have a variety of arrhythmias, including AV block, atrial tachycardia, junctional tachycardia.

**RESULTS**

A total of 730 patients were taken the patients randomly and were divided into two groups: the first group Digoxen, which has a narrow therapeutic index More than ≥ 25 years 190 patient maintenance dose 0.125 – 0.25mg one daily loading dose 500µg one daily or 250 µg tow daily digoxin bioavailability oral 75% therapeutic range 0.6 to 2nmol / L onset of action 30 to 120 minutes peak 6-8 hours effect IV 5-30 minutes elimination 36- 48 hours and rest period of medication 1 day the result successfully, either material Acetaminophen therapeutic index wide the number 540 patient therapeutic dose in adults is 1- 4 g/day , The minimum lethal dose in adults is 5 -15 g ; the acute lethal dose ranges from 13 to 25 g , We used 1500 mg daily safely, Therapeutic blood (its serum or plasma) concentrations range from 5 to 20 mg/l. The drug risk ratio was 0.50 for NTI-drugs and 0.20 for non-NTI-drugs. Use optimal dose . Among the results of applied research to assess cardiac safety using digoxin at a dose of 0 ,125 – 0 ,25 mg and controlled and prevention of Atrial fibrillation AF, the maximum increase in QRS from baseline was 13.2% with the calculation of high blood pressure risk factors and increased cardiomyopathy, and six patients had Only they have a maximum value greater than >100 msc QRS are under intensive treatment, The most frequent drug-related proarrhythmic effects were bradycardia (13.2 %), ventricular extrasystoles (10.6 %), AV block (4.0 %), supra-ventricular tachycardia (2.2 %), bundle branch block (1.8 %) and AF (1.3 %). New or worsened arrhythmias occurred in 1 % of patients with PSVT and in 0.4 % of patients with paroxysmal AF/flutter treated with iv in fluid digoxin or verapamil.
under control, while (6.5%) of patients with chronic AF developed ventricular tachyarrhythmia; therefore, digoxin is not recommended in these patients.

Discussion
Drug-related problems (DRPs) have been found to be associated with increased morbidity, mortality and health costs. Thus, preventing DRPs will benefit both patients and the community. Drugs with a narrow therapeutic index (NTI-drugs) are drugs with slight differences between their therapeutic and toxic doses, which means that small changes in dosage or interactions with other drugs can cause adverse effects. NTI drugs have been proven to be the main cause of emergency department visits. Many hospitalized patients have severe illness and have conditions that may affect the pharmacokinetics and pharmacodynamics of the drugs administered to them. Accordingly, hospitalization may increase the risk of DRPs, and patients using NTI drugs are more likely to be at special risk. However, the relationship between the use of NTI drugs and the incidence of different DRPs in hospitalized patients is unknown. The study aims to explore how and to what extent NTI drugs, compared to other drugs, are associated with DRP antagonists in hospitalized patients, moreover, to develop a tool to calculate the risk of DRPs. A prospective multicenter design was applied. The range between the ED50 and TD50 can be considerable, The US Food and Drug Administration (FDA) defines a drug product as having an NTI when (a) there is less than a twofold difference in median lethal dose (LD50) and median effective dose values (ED50) or (b) there is less than a twofold difference in the minimum toxic concentrations (MTC) and minimum effective concentrations (MEC) in the blood and (c) safe and effective use of the drug requires careful titration and patient monitoring 2018.

Conclusion
We conducted a study to evaluate the clinical work of the physician and the clinical pharmacist to provide accuracy in dealing with the most serious danger in various departments of the hospital and to monitor drug concentration in ambulatory patients receiving NTR drugs. The objectives of this study were to describe the proportion of patients discharged from NTR drugs who did not have control of drug concentration during the one-year treatment period and to identify patient characteristics associated with lack of control. The results of this study provide information to guide the thoughtful establishment of quality care indicators related to NTR drug control in ambulatory patients. The aim of therapeutic drug monitoring is to guide doses by measurements of drug concentration. Therapeutic drug monitoring is useful for drugs that lack the association between dosage and pharmacokinetic properties, because the presence of digoxin drugs have low thyrbitic index when used for specific diseases of congestive heart failure, atrial tremor, myocardial dysfunction and caveats and drug interactions with them and to the optimal dose, and compared with Acetaminophen (paracetamol, which has a wide therapeutic index and a far-reaching toxicity ratio, are treated as different examples of real life treatment and security.

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