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Clinical Chemistry (Chemical Pathology, Clinical Biochemistry or Medical Biochemistry)

Ganga Shy Meena

Assistant Professor, Chemistry, SCRS Govt. College, Sawai Madhopur, Rajasthan, India

ABSTRACT: Clinical chemistry (also known as chemical pathology, clinical biochemistry or medical biochemistry) is the area of chemistry that is generally concerned with analysis of bodily fluids for diagnostic and therapeutic purposes. It is an applied form of biochemistry (not to be confused with medicinal chemistry, which involves basic research for drug development).

The discipline originated in the late 19th century with the use of simple chemical reaction tests for various components of blood and urine. In the many decades since, other techniques have been applied as science and technology have advanced, including the use and measurement of enzyme activities, spectrophotometry, electrophoresis, and immunoassay. There are now many blood tests and clinical urine tests with extensive diagnostic capabilities.

Most current laboratories are now highly automated to accommodate the high workload typical of a hospital laboratory.[1] Tests performed are closely monitored and quality controlled.

All biochemical tests come under chemical pathology. These are performed on any kind of body fluid, but mostly on serum or plasma. Serum is the yellow watery part of blood that is left after blood has been allowed to clot and all blood cells have been removed. This is most easily done by centrifugation, which packs the denser blood cells and platelets to the bottom of the centrifuge tube, leaving the liquid serum fraction resting above the packed cells. This initial step before analysis has recently been included in instruments that operate on the "integrated system" principle. Plasma is in essence the same as serum, but is obtained by centrifuging the blood without clotting. Plasma is obtained by centrifugation before clotting occurs. The type of test required dictates what type of sample is used.

A large medical laboratory will accept samples for up to about 700 different kinds of tests. Even the largest of laboratories rarely do all these tests themselves, and some must be referred to other labs.

This large array of tests can be categorised into sub-specialities of:

- General or routine chemistry – commonly ordered blood chemistries (e.g., liver and kidney function tests).
- Special chemistry - elaborate techniques such as electrophoresis, and manual testing methods.
- Clinical endocrinology – the study of hormones, and diagnosis of endocrine disorders.
- Toxicology – the study of drugs of abuse and other chemicals.
- Therapeutic Drug Monitoring – measurement of therapeutic medication levels to optimize dosage.
- Urinalysis – chemical analysis of urine for a wide array of diseases, along with other fluids such as CSF and effusions
- Fecal analysis – mostly for detection of gastrointestinal disorders.

KEYWORDS: clinical, chemistry, pathology, biochemistry, medical, chemical, toxicology, endocrinology

I. INTRODUCTION

In sub branch of clinical chemistry - endocrinology, medical emergencies include diabetic ketoacidosis, hyperosmolar hyperglycemic state, hypoglycemic coma, acute adrenocortical

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Volume 3, Issue 7, July 2020

insufficiency, phaeochromocytoma crisis, hypercalcemic crisis, thyroid storm, myxoedema coma and pituitary apoplexy.[3]

Emergencies arising from decompensated pheochromocytomas or parathyroid adenomas are sometimes referred for emergency resection when aggressive medical therapies fail to control the patient's state, however the surgical risks are significant, especially blood pressure lability and the possibility of cardiovascular collapse after resection (due to a brutal drop in respectively catecholamines and calcium, which must be compensated with gradual normalization).[4][5] It remains debated when emergency surgery is appropriate as opposed to urgent or elective surgery after continued attempts to stabilize the patient, notably in view of newer and more efficient medications and protocols

Toxicology is a scientific discipline, overlapping with biology, chemistry, pharmacology, and medicine, that involves the study of the adverse effects of chemical substances on living organisms[1] and the practice of diagnosing and treating exposures to toxins and toxicants. The relationship between dose and its effects on the exposed organism is of high significance in toxicology. Factors that influence chemical toxicity include the dosage, duration of exposure (whether it is acute or chronic), route of exposure, species, age, sex, and environment. Toxicologists are experts on poisons and poisoning. There is a movement for evidence-based toxicology as part of the larger movement towards evidence-based practices. Toxicology is currently contributing to the field of cancer research, since some toxins can be used as drugs for killing tumor cells. One prime example of this is ribosome-inactivating proteins, tested in the treatment of leukemia.[2]

The word toxicology (/ˌtɒksɪˈkɒlədʒi/) is a neoclassical compound from New Latin, first attested circa 1799,[3] from the combining forms toxico- + -logy, which in turn come from the Ancient Greek words τοξικός toxikos, "poisonous", and λόγος logos, "subject matter").

The goal of toxicity assessment is to identify adverse effects of a substance.[11] Adverse effects depend on two main factors: i) routes of exposure (oral, inhalation, or dermal) and ii) dose (duration and concentration of exposure). To explore dose, substances are tested in both acute and chronic models.[12] Generally, different sets of experiments are conducted to determine whether a substance causes cancer and to examine other forms of toxicity.[12]

Factors that influence chemical toxicity:[8]

- Dosage
  - Both large single exposures (acute) and continuous small exposures (chronic) are studied.
- Route of exposure
  - Ingestion, inhalation or skin absorption
- Other factors
  - Species
  - Age
  - Sex
  - Health
  - Environment
  - Individual characteristics

The discipline of evidence-based toxicology strives to transparently, consistently, and objectively assess available scientific evidence in order to answer questions in toxicology,[13] the study of the adverse effects of chemical, physical, or biological agents on living organisms and the environment, including the prevention and amelioration of such effects.[14] Evidence-based toxicology has the potential to address concerns in the toxicological community about the limitations of current approaches to assessing the state of the science.[15][16] These include concerns related to transparency in decision making, synthesis of different types of evidence, and the assessment of bias and credibility. Evidence-based toxicology has its roots in the larger movement towards evidence-based practices.

Most chemicals display a classic dose response curve – at a low dose (below a threshold), no effect is observed.[8]:80 Some show a phenomenon known as sufficient challenge – a small exposure produces animals that "grow more rapidly, have better general appearance and coat quality, have fewer tumors, and live longer than the control animals".[35] A few chemicals have no well-defined safe level of exposure. These are treated with special care. Some chemicals are subject to bioaccumulation as they are stored in rather than being excreted from the body;[8]:85–90 these also receive special consideration.

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Volume 3, Issue 7, July 2020

Several measures are commonly used to describe toxic dosages according to the degree of effect on an organism or a population, and some are specifically defined by various laws or organizational usage. These include:

- LD50 = Median lethal dose, a dose that will kill 50% of an exposed population
- NOEL = No-Observed-Effect-Level, the highest dose known to show no effect
- NOAEL = No-Observed-Adverse-Effect-Level, the highest dose known to show no adverse effects
- PEL = Permissible Exposure Limit, the highest concentration permitted under US OSHA regulations
- STEL = Short-Term Exposure Limit, the highest concentration permitted for short periods of time, in general 15–30 minutes
- TWA = Time-Weighted Average, the average amount of an agent's concentration over a specified period of time, usually 8 hours
- TTC = The Threshold of Toxicological Concern concept[36] has been applied to low-level contaminants, such as the constituents of tobacco smoke

Medical toxicology is the discipline that requires physician status (MD or DO degree plus specialty education and experience).

Clinical toxicology is the discipline that can be practiced not only by physicians but also other health professionals with a master's degree in clinical toxicology: physician extenders (physician assistants, nurse practitioners), nurses, pharmacists, and allied health professionals.

Forensic toxicology is the discipline that makes use of toxicology and other disciplines such as analytical chemistry, pharmacology and clinical chemistry to aid medical or legal investigation of death, poisoning, and drug use. The primary concern for forensic toxicology is not the legal outcome of the toxicological investigation or the technology utilized, but rather the obtainment and interpretation of results.

Computational toxicology is a discipline that develops mathematical and computer-based models to better understand and predict adverse health effects caused by chemicals, such as environmental pollutants and pharmaceuticals. Within the Toxicology in the 21st Century project, the best predictive models were identified to be Deep Neural Networks, Random Forest, and Support Vector Machines, which can reach the performance of in vitro experiments. Occupational toxicology is the application of toxicology to chemical hazards in the workplace.

II. DISCUSSION

Toxicologists perform many different duties including research in the academic, nonprofit and industrial fields, product safety evaluation, consulting, public service and legal regulation. In order to research and assess the effects of chemicals, toxicologists perform carefully designed studies and experiments. These experiments help identify the specific amount of a chemical that may cause harm and potential risks of being near or using products that contain certain chemicals. Research projects may range from assessing the effects of toxic pollutants on the environment to evaluating how the human immune system responds to chemical compounds within pharmaceutical drugs. While the basic duties of toxicologists are to determine the effects of chemicals on organisms and their surroundings, specific job duties may vary based on industry and employment. For example, forensic toxicologists may look for toxic substances in a crime scene, whereas aquatic toxicologists may analyze the toxicity level of water bodies.

Therapeutic drug monitoring (TDM) is a branch of clinical chemistry and clinical pharmacology that specializes in the measurement of medication levels in blood. Its main focus is on drugs with a narrow therapeutic range, i.e. drugs that can easily be under- or overdosed.[1] TDM aimed at improving patient care by individually adjusting the dose of drugs for which clinical experience or clinical trials have shown it improved outcome in the general or special populations. It can be based on a a priori pharmacogenetic, demographic and clinical information, and/or on the a posteriori measurement of blood concentrations of drugs (pharmacokinetic monitoring) or biological surrogate or end-point markers of effect (pharmacodynamic monitoring).[2]

There are numerous variables that influence the interpretation of drug concentration data: time, route and dose of drug given, time of blood sampling, handling and storage conditions, precision and accuracy of the analytical method,

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Volume 3, Issue 7, July 2020

validity of pharmacokinetic models and assumptions, co-medications and, last but not least, clinical status of the patient (i.e. disease, renal/hepatic status, biologic tolerance to drug therapy, etc.).[3]

Many different professionals (physicians, clinical pharmacists, nurses, medical laboratory scientists, etc.) are involved with the various elements of drug concentration monitoring, which is a truly multidisciplinary process. Because failure to properly carry out any one of the components can severely affect the usefulness of using drug concentrations to optimize therapy, an organized approach to the overall process is critical.[3]

In pharmacotherapy, many medications are used without monitoring of blood levels, as their dosage can generally be varied according to the clinical response that a patient gets to that substance. For certain drugs, this is impracticable, while insufficient levels will lead to undertreatment or resistance, and excessive levels can lead to toxicity and tissue damage.

Indications in favor of therapeutic drug monitoring include:[4][5]

- consistent, clinically established pharmacodynamic relationships between plasma drug concentrations and pharmacological efficacy and/or toxicity;
- significant between-patient pharmacokinetic variability, making a standard dosage achieve different concentration levels among patients (while the drug disposition remains relatively stable in a given patient);
- narrow therapeutic window of the drug, which forbids giving high doses in all patients to ensure overall efficacy;[6]
- drug dosage optimization not achievable based on clinical observation alone;
- duration of the treatment and criticality for patient's condition justifying dosage adjustment efforts;
- potential patient compliance problems that might be remedied through concentration monitoring.

TDM determinations are also used to detect and diagnose poisoning with drugs, should the suspicion arise.

Examples of drugs widely analysed for therapeutic drug monitoring:[1]

- Aminoglycoside antibiotics (gentamicin)
- Antiepileptics (such as carbamazepine, phenytoin and valproic acid)
- Mood stabilisers, especially lithium citrate
- Antipsychotics (such as pimozide and clozapine)
- Digoxin
- Ciclosporin, tacrolimus in organ transplant recipients

TDM increasingly proposed for a number of therapeutic drugs, e.g. many antibiotics, small molecule tyrosine kinase inhibitors and other targeted anticancer agents, TNF inhibitors and other biological agents, antifungal agents, antiretroviral agents used in HIV infection, psychiatric drugs[7] etc.

Urinalysis, a portmanteau of the words urine and analysis,[1] is a panel of medical tests that includes physical (macroscopic) examination of the urine, chemical evaluation using urine test strips, and microscopic examination. Macroscopic examination targets parameters such as color, clarity, odor, and specific gravity; urine test strips measure chemical properties such as pH, glucose concentration, and protein levels; and microscopy is performed to identify elements such as cells, urinary casts, crystals, and organisms.[2]

Urine is produced by the filtration of blood in the kidneys. The formation of urine takes place in microscopic structures called nephrons, about one million of which are found in a normal human kidney. Blood enters the kidney though the renal artery and flows through the kidney's vasculature into the glomerulus, a tangled knot of capillaries surrounded by Bowman's capsule. The glomerulus and Bowman's capsule together form the renal corpuscle. A healthy glomerulus allows many solutes in the blood to pass through, but does not permit the passage of cells or high-molecular weight substances such as most proteins. The filtrate from the glomerulus enters the capsule and proceeds to the renal tubules, which reabsorb water and solutes from the filtrate into the circulation and secrete substances from the blood into the urine in order to maintain homeostasis.[3][4]

The first destination is the proximal convoluted tubule. The filtrate proceeds into the loop of Henle, then flows through the distal convoluted tubule to the collecting duct. The collecting ducts ultimately drain into the renal calyces, which

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Volume 3, Issue 7, July 2020

lead to the renal pelvis and the ureter. Urine flows through the ureters into the bladder and exits the body through the urethra.[5][6]

Besides excreting waste products, the process of urine formation helps to maintain fluid, electrolyte and acid-base balance in the body. The composition of urine reflects not only the functioning of the kidneys, but numerous other aspects of the body's regulatory processes.[7] The ease with which a urine sample can be obtained makes it a practical choice for diagnostic testing.[8]

IV. RESULTS

Urinalysis involves assessment of the physical properties of urine, such as color and clarity; chemical analysis using urine test strips; and microscopic examination.[9] Test strips contain pads impregnated with chemical compounds that change color when they interact with specific elements in the sample, such as glucose, protein and blood,[10] and microscopic examination permits the counting and classification of solid elements of the urine, such as cells, crystals, and bacteria.[11]

Urinalysis is one of the most commonly performed medical laboratory tests.[12] It is frequently used to help diagnose urinary tract infections[13] and to investigate other issues with the urinary system, such as incontinence.[14] It may be used to screen for diseases as part of a medical assessment. The results can suggest the presence of conditions such as kidney disease, liver disease and diabetes.[12] In emergency medicine urinalysis is used to investigate numerous symptoms, including abdominal and pelvic pain, fever,[17] and confusion.[18] During pregnancy, it may be performed to screen for protein in the urine (proteinuria), which can be a sign of pre-eclampsia,[19] and bacteria in the urine, which is associated with pregnancy complications.[16][20] The analysis of urine is invaluable in the diagnosis and management of kidney diseases.[21]

Samples for urinalysis are collected into a clean (preferably sterile) container.[8][22] The sample can be collected at any time of the day,[23] but the first urine of the morning is preferred because it is more concentrated.[24] To prevent contamination, a "midstream clean-catch" technique is recommended, in which the genital area is cleaned before urinating and the sample is collected partway through the urination.[22] Samples can also be collected from a urinary catheter or by inserting a needle through the abdomen and into the bladder (suprapubic aspiration).[25] In infants and young children, urine may be collected into a bag attached to the genital region, but this is associated with a high risk of contamination.[8] If the sample is not tested promptly, inaccurate results can occur because bacteria in the urine will multiply and elements such as cells and casts will degrade. It is recommended that urinalysis is performed within two hours of sample collection if the urine is not refrigerated.

Normal urine has a yellow hue, which is primarily caused by the pigment urochrome. The color can range from pale yellow to amber based on the individual's hydration status. Urine can develop a variety of abnormal colors, which may suggest disease in some cases.[26] A total lack of color indicates that the urine is extremely dilute, which may be caused by excessive fluid intake, diabetes insipidus, or diabetes mellitus. Dark yellow-brown to green urine may suggest a high concentration of bilirubin, a state known as bilirubinuria. Red urine often indicates the presence of red blood cells or hemoglobin, but can also be caused by some medications and the consumption of foods containing red pigments,[26] such as beets. Myoglobin, a product of muscle breakdown, can give urine a red to reddish-brown color.[28] Dark brown or black urine can occur in a genetic disorder called alkaptonuria and in people with melanoma.[29] Purple urine occurs in purple urine bag syndrome.[30]

A spectrum of abnormal colors can result from the intake of drugs. An unusually bright yellow color can occur after consumption of B vitamin supplements,[31] while phenazopyridine, used to treat urinary tract-related pain, can turn the urine orange. Methylene blue may turn it blue to bluish-green.[32] Phenolphthalein, a stimulant laxative previously found in Ex-Lax,[33] can produce colors ranging from red to purple, and levodopa, used to treat Parkinson's disease, may result in "cola-colored" urine.[27]

The clarity of urine is also recorded during urinalysis. Urine is typically clear; materials such as crystals, cells, bacteria, and mucus can impart a cloudy appearance.[26] A milky appearance can be caused by a very high concentration of white blood cells or fats, or by chyluria (the presence of lymphatic fluid in the urine).[34] Unpreserved urine will become cloudier over time.[35]

The odor (scent) of urine can normally vary from odorless (when very light colored and dilute) to a much stronger odor when the subject is dehydrated and the urine is concentrated.[36] Transient changes in urine odor can occur after consuming certain foods, most notably asparagus. The urine of diabetics experiencing ketoacidosis (urine containing

high levels of ketone bodies) may have a fruity or sweet smell, while urine from individuals with urinary tract infections often has a foul smell. Some inborn errors of metabolism cause characteristic odors, such as maple syrup urine disease (which takes its name from the urine scent) and phenylketonuria (which causes a "mousey" smell).[37] Odor is rarely reported during urinalysis.[38] Specific gravity is a measure of the concentration of the urine, which provides information about hydration status and kidney function. It normally ranges from 1.003 to 1.035; lower values indicate that the urine is dilute, while higher values mean that it is concentrated. A urine specific gravity that consistently remains around 1.010 (isosthenuria) can indicate kidney damage, as it suggests that the kidneys have lost the ability to control urine concentration.[39] It is not possible for the kidneys to produce urine with a specific gravity greater than 1.040[40] but such readings can occur in urine that contains high-molecular weight substances, such as contrast dyes used in radiographic imaging. Specific gravity is commonly measured with urine test strips, but refractometers may also be used. Reagent strip readings are based on the concentration of ions in the sample, while refractometer readings are affected by other substances such as glucose and protein.

V. CONCLUSIONS

Urine test strips or "dipsticks" allow for the rapid measurement of numerous urine parameters and substances. The strip is dipped into the urine sample and the color changes on the reagent pads are read after a defined period of time, either by eye or using an automated instrument.[43] The tests included vary depending on the type of dipstick, but common ones are glucose, ketones, bilirubin, urobilinogen, blood, white blood cells (leukocyte esterase), protein, nitrite, pH, and specific gravity. Nitrite is reported as negative or positive;[46] other elements may be scored on a scale or reported as an approximate concentration based on the intensity of the color change. False positive and false negative results may occur. General sources of error include abnormally colored urine, which interferes with the interpretation of color changes; high levels of ascorbic acid (Vitamin C), which can cause false negative results for blood, bilirubin, glucose, and nitrite; and variations in the concentration of the sample. Various compounds in the urine can precipitate to form crystals. The composition of crystals can be identified based on their appearance and the pH of the urine (many types preferentially form at an acidic or alkaline pH). Crystals that can be found in normal urine include uric acid, monosodium urate, triple phosphate (ammonium magnesium phosphate), calcium oxalate, and calcium carbonate. Crystals can also appear as poorly defined aggregates of granular material, termed amorphous urates or amorphous phosphates (urates form in acid urine while phosphates form in alkaline urine). These are of no clinical significance, but they can interfere with microscopy by obscuring other elements (especially bacteria).[126] Some drugs, such as sulfonamides, may form crystals when excreted in the urine, and ammonium biurate crystals commonly occur in aged samples.

The presence of crystals in the urine has conventionally been associated with the formation of kidney stones, and crystalluria is more common in people with kidney stones than those without. However, crystalluria occurs in up to 20% of the normal population, so it is not a reliable diagnostic marker. Some types of crystals are characteristically associated with disease states. Leucine and tyrosine crystals may be observed in liver disease,[24] and cystine crystals indicate cystinuria (although they look identical to hexagonal variants of uric acid crystals, and can only be distinguished with further testing).[128] Cholesterol crystals may rarely be seen in nephrotic syndrome and chyluria

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