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A Broad Review On Various Drug Evaluation Methods

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Abstract :

Adult and pediatric populations have distinct medication pharmacokinetics and pharmacodynamics with the latter being more variable. While these variations in pharmacokinetics and pharmacodynamics support particular research, they also bring up a variety of moral and practical concerns. The invasiveness of the procedures and the barriers to patient recruitment are the main practical challenges to overcome while conducting clinical research in children. The Classical pharmacokinetic studies cannot often be performed on children due to the invasiveness associated with pain/anxiety and blood loss, especially in neonates and infants. Pharmacokinetic , pharmacodynamic modeling-based population techniques are especially attractive for pediatric populations due to their ability to handle sparse data. It has previously been highlighted how important population techniques are for examining dose-concentration-effect correlations and for qualitatively and quantitatively evaluating variables that could account for interindividual variability.

Key word:

Screening methods ,Drug studies, In vivo-vitro studies, Animal cell culture Technique.

Introduction :

Analgesics work by selectively reducing pain without altering consciousness by interacting with peripheral and central nervous system pain mediators. An analgesic can be a narcotic or a non-prescription analgesic. An analgesic is one of the most important defence mechanisms in the body that tells us when something is wrong. There are two main types of pain: acute pain and chronic pain Acute pain is pain that is repeated and goes away within a short amount of time, whether treated or not Chronic pain, on the other hand, is pain that develops over a long period of time and goes away slowly or not at all Both the central and peripheral nervous systems are involved in the perception of pain, from its source to its point of reception Pain relief depends on several factors, including: type of pain where the pain originates whether the pain originates from the nervous system whether neurogenic pain occurs as a result of anxiousness depression emiasiasia epilepsy seizure disorder phobia traumatic pain on the other hand, opioid analgesics are the most commonly used.[1] Pain is a complex and uniquely personal experience, involving various physiological and perceptual pathways and factors. Pain is then accordingly described as perceiving nociception, whether arising from the nociceptors (nociceptive pain), the nerve itself (neuropathic pain), or a combination of the two (mixed pain).[2]

Analgesic activity:

Analgesics are substances that, without altering awareness, selectively reduce pain by acting on peripheral and CNS pain mediators. While analgesics can be either narcotic or non-narcotic, they are one of the most vital defence mechanisms in our bodies that alert us to abnormalities.

Classification:

A. Nonselective COX inhibitors (traditional NSAIDs):
1. Salicylates: Aspirin.
2.Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. Fenamate: Mephenamic acid.
4.Enolic acid derivatives: Piroxicam, Tenoxicam.
5.Acetic acid derivatives: Ketorolac, Indomethacin, Nabumetone.
6. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone
B. Preferential COX-2 inhibitors: Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac.
C.Selective COX-2 inhibitors :Celecoxib, Etoricoxib, Parecoxib.
D.Analgesic-antipyretics with poor antiinflammatory action:
1. Para aminophenol derivative: Paracetamol (Acetaminophen).
2.Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone.
3. Benzoxazocine derivative: Nefopam.
E.Opoids:
1.Natural opium alkaloid:morphine,codeine
2.Semisynthetic opiates:diacetylmorphine,pholcodeinme,ethylmorphine. [3]

Mechanism of action:

The NSAIDs comprise a heterogenous group of six major chemical classes of drugs that are primarily used as anti-inflammatory agents. The main mechanism of action of NSAIDs is inhibition of the formation of prostaglandins (as well as prostacyclin and thromboxane) from arachidonic acid via inhibition of cyclooxygenase enzymes 1 and 2 (COX-1 and COX-2, also known as prostaglandin synthase.The nomenclature of the COX enzymes is slightly misleading, as the synthase enzyme has both a cyclooxygenase (COX) and a peroxidase (POX) binding site.

Figure 1:

NSAID-mediated COX inhibition
COX - Cyclooxygenase
Coxib - Selective COX-2 inhibitor
NSAIDs - Nonsteroidal anti-inflammatory drugs

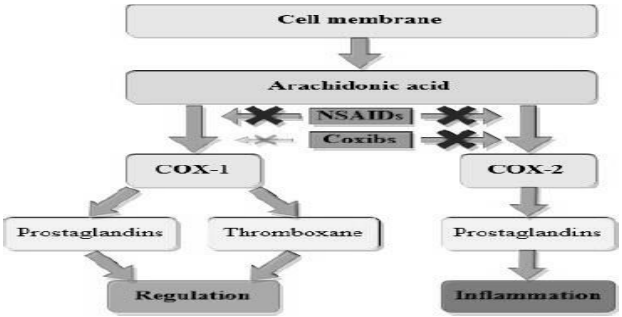

Fig.1[2]

The COX-1 enzyme is variably expressed in nearly all tissues, and is responsible for regulating normal cellular processes. COX-2 is generally undetectable in most tissues except for its constitutive expression in the brain, kidney, and bone but is highly inducible in states of inflammation, leading to the production of pro-inflammatory prostaglandins. While many processes contribute to the establishment of inflammation, the prostaglandins are putatively accepted as the primary inflammatory mediators. The various downstream effects of prostaglandin synthesis depend on the differential expression of COX-1 and COX-2 enzymes in different tissues at the sites of inflammation.
NSAIDs exert their effect through the inhibition of COX enzymes, thereby reducing the production of prostaglandins and diminishing nociceptive signal transduction. The selection and degree of COX inhibition varies, however, depending on the NSAID used.[2]

Evaluation Models for Analgesic Activity:

Methods of Assessing Pain-relieving Effects:

Evaluation is a necessary stepin the research and clinical testing of any analgesic medication. Experiments have b een conducted on different animal models in laboratory s ettings.The administration or implementation of the med ication or plan is being tested. Selecting a model is not s olely based on one uniform underlying theory, as there c an be variations among different models.
Choosing the appropriate model necessitates thoughtful deliberation. It was discovered that only two commonly employed techniques were utilized:

In Vivo Methods:
Hot plate method
Cold tail flick test

Hot Plate Method:

Cold tail fick test:

The thermal stimulus principle is the foundation of the hot spread plate of analgesic assessment. The pain was first induced in the animal utilised in this process by heating its paw. This will hurt the rats, who will then begin to lick their paws and attempt to balance on one leg for a brief period of time before receiving the drug or plan extract that will be tested. Consistently keeping the hot plate temperature at 55°C is required. The following systematic process is followed:

1. Weigh and count the experimental mice and rats.
2. Animals were divided into three groups.
3. After placing the animal on the hot plate, observe the animal's licking or jumping response to note the rat's reaction time.
4. A 15-second time limit will be set as the cutoff to prevent needless suffering and damage.
5. After injecting the medicine (plant extract) into the experimental animal, let it dissolve, and then put them back on a hot plate, record the baseline reaction time.
6. Evaluate the reaction time prior to and following medication insertion.
7. If the technique does not produce good results or results, repeat again

Purpose and Rationale

Heat is employed as the noxious stimuli in the tail flick test. The length of time it takes the creature to flick its tail is a dependent variable. The morphine-like medications have the ability to increase the reaction time.

Procedure:

Mice (18 to 22 g) are housed in a compact cage. Letting the tail hang out The radiation source is kept at the proper temperature. The mouse's tail is put on the radiation source, and the length of time it takes the mice to remove their tail
is timed. The typical withdrawal period is 2 to 10 seconds.Before and after the delivery of the standard or test substance, the rear latency is measured.

In Vitro Methods:

3H-Naloxone binding assay
Purpose and Rationale:
It has been demonstrated that there is a strong link between the in vivo pharmacological efficacy of opiate antagonists and agonists and their capacity to displace radiolabeled naloxone. The development of an assay to classify substances as opiod agonists, mixed agonist-antagonists, and adversaries by deciding the IC50 values for 3H-Naloxone in the absence or presence of Na+ was prompted by the later discovering that Na+ (100 mM) improves the binding of adversaries and lessens the binding of agonists.

Procedure:

[N-allyl-2,3-3H] You may buy naloxone (38-58 Ci/mmol) at New England Nuclear.
3H-naloxone is produced up to a level of 100 nM for ICso measurements, and 50 l is added to every tube, resulting in a final concentration of 5 nM in the test. Hoffmann LaRoche is the source of levorphanol tartrate. In distilled water, a stock solution containing 0.1m levorphanol is prepared. To assess stereospecific binding, this stock is dilute 1:200 in distilled water, and 20 l is added to 3 tubes. This results in a final level of 0.1 M in the experiment.
Hoffmann LaRoche is the source of dextrorphan tartrate. In distilled water, a stock solution containing 0.2 mm dextrophan is prepared. The tubes containing the different test drug concentrations as well as the tubes measuring total binding receive 20 l of this stock after it has been dilute 1:200 in distilled water.

3H-Dihydromorphine Binding to μ Opiate Receptors in Rat Brain:

Purpose and Rationale:
Opioid receptors are thought to mediate their supraspinal action. The u receptor, a high affinity opiate binding site, is one of the receptors that 3H-dihydromorphine (3H-DHM) shows some selectivity for. The assay is used to identify substances that prevent the binding of 3H-DHM in a rat brain synaptic membrane preparation.

Procedure:

[1,7,8-3H] Dihydromorphine (H-DHM) is purchased from Amersham and has a specific activity of 69 Ci/mmol. A stock solution of 20 nM is prepared for ICs measurements. In order to achieve a pure product of 50 μm inside the 2 ml assay, fifty um are added to every test tube. To determine non-specific binding, levallorphan tartrate is utilised. In deionized water, a 0.1 m M sample solution is made. A concentration of total of 0.1 M in the μl assay is produced by adding 20 l to each of the three tubes. The test compounds are dissolved in a suitable solvent to form a 1 m M stock solution, which is serially diluted until the final assay concentrations range from 106 to 109 M. For each, at least seven concentrations are employed.[4]

Respiratory activity:

Anti-asthamatic activity:

Introduction:

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosa edema and mucus plugging.

Classification:

1.Bronchodilators:
Sympathomimetics :
Short Acting: Salbutamol, Terbutaline
Long Acting: Formeterol, Salmetrol, Bambuterol
Methylxanthine: Aminophylline, Theophylline
2.Anticholinergics: Ipratropium, Oxytropiu, Tiotropium
3.Mast cell stabilizers: Sod Cromoglycate kitotifenI
4.Corticosteroids:
Systemic: Hydrocortisone Prednisolone Other glucocorticoids
Inhalational:Beclomethasone dipropional Budesonide Fluticasone propionate
5.Anti- igE antibody:omalizumab. [3]

Screening method:

The Antiasthmatic Test In Vivo*:* To screen the sensitivity, guinea pigs were placed in a glass chamber and sprayed with the mixture of 0.1% histamine and 2% acetylcholine chloride under the average pressure of mmHg for 15.The times to onset of respiratory distress and tumble (preconvulsive time) were recorded. The guinea pigs with preconvulsive time of more than 120 s were considered to be insensitive and discarded. The eligible guinea pigs were randomly allotted to groups and administered according to Section for 5 days. The administration on day 5 was given at 1.5 h before the measurement of preconvulsive time. The delitescence of convulsion and tumble for each guinea pig within 6 min were observed.

In-vitro models:

Isolated goat tracheal chain preparation:

This method is applied for the subject of the action of antispasmodic drugs on the tracheal musculature. The method is based upon the findings that the excised goat trachea respond to many drugs with the characteristic actions for which the drugs are well known, and that with proper magnification, the response can be recorded and measured for comparative purposes. Although, this method is known for its suitability in the study of antispasmodic drugs in general, emphasis is given on its use in the testing of bronchodilators. This is because of the close anatomical and physiological association, which exists between tracheal and bronchial musculature. In isolated goat tracheal preparation, there is preponderance of H1 excitatory and a scanty population of H2 inhibitory receptors. Acetylcholine, histamine, 5- hydroxytryptamine and bradykinin show dose relative contractile responses on isolated goat trachea. With these agonists, the concentration necessary to produce contraction is less with goat tracheal chain than with guinea pig tracheal chain. Both goat tracheal chain and strip preparation were suitable for screening spasmogenic activity on respiratory smooth muscle and goat tracheal chain is easier to handle and prepare and is also much more sensitive than guinea-pig tracheal chain. It is reported that 12 isolated goat trachea contracts in response g), histamine in a dose dependentand barium chloride manner and to 5-HT in a narrow dose range. Chlorpheniramine maleate blocks contractions due to histamine while cimetidine potentiates the contraction [4]

Anti-tussive activity:

Definition: Antitussives are prescription or over-the-counter drugs used for suppressing cough. Antitussives act on the cough center in the brain and decrease the sensitivity of cough receptors.

Classification :
Antitussives (Cough centre suppressants):
Opioids: Codeine, Ethylmorphine, Pholcodeine.
Nonopioids: Noscapine, Dextromethorphan, Chlophedianol.
Antihistamines: Chlorpheniramine, Diphenhydramine, Promethazine.
Peripherally acting: Prenoxdiazine

Screening method:

Antitussive Test In Vivo*:*

To screen the sensitivity, mice were placed in a glass chamber (0.5 L) and sprayed with 25% aqueous ammonia (w/v) under the average pressure of 400 ± 50 mmHg for 5 s. The mice were randomly allotted to eight groups (n = 10) and administered according to Section 2.3. All groups were treated with a single dose daily for 7 days and the last dose was given 1.5 h before the measurement of latent period of cough (from the start to the onset of cough) and frequency of cough. The frequency of cough was observed for 2 min.

In vitro free radical scavenging activity using 1-diphenyl-2-picryl-hydrazyl method:

The free radical scavenging activity (FRSA) of TDEE was measured by DPPH method. 0.1 mM solution of DPPH was prepared in methanol, and 1 ml of it was

added to different concentrations of TDEE (50, 100, 200, 400, and 500 µg/ml) and the final volume of 3 ml was made with methanol. The mixture was shaken vigorously and incubated at room temperature for 30 min. Absorbance of the resulting mixture was measured at 517 nm against methanol as blank, using a ultraviolet-visible spectrophotometer.Each sample was evaluated in triplicate and results were represented as mean. The ascorbic acid was used as a standard antioxidant in this method.[4]

Anticancer activity :

The anticancer drugs either kill cancer cells or modify their growth.
One of the most fascinating fields of study has been cancer research, and its diversity is what makes it so fascinating.

Classification:

A.Cytotoxic drugs:
1.Alkylating agents: Mechlorethamine
Nitrogen mustard : (Mustine HCl) Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan Ethylenimine: Thio-TEPA
Alkyl sulfonate:Busulfan
Nitrosourea : Carmustine (BCNU), Lomustine (CCNU)
Triazine:Dacarbazine (DTIC), Temozolomide
Methylhydrazine: Procarbazine
2.Platinum coordination complexes: OxaliplatinCarboplatin,carboplatin
3.Antimetabolites:
Folate antagonist :Methotrexate (Mtx) Pemetrexed
Purine antagonist:6-Thioguanine(6-TG),Azathioprine,6-Mercaptopurine(6-MP), Fludarabine.
Pyrimidine antagonist: 5-Fluorouracil (5-FU),Capecitabine,Cytarabine
4.Microtubule damaging agents:
Vincristine (Oncovin), Vinblastine, Vinorelbine
Paclitaxel, Docetaxel Estramustine
5.Topoisomerase-2 inhibitors: Etoposide
6.Topoisomerase-1 inhibitors :Topotecan Irinotecan
7.Antibiotics: Actinomycin D (Dactinomycin), Doxorubicin, Daunorubicin (Rubidomycin), Mitoxantrone, Bleomycins, Mitomycin C
Miscellaneous: Hydroxyurea, L-Asparaginase, Tretinoin, Arsenic trioxide

B. Targeted drugs:
1.Tyrosine protein kinase inhibitors: imatinib, Nilotinib
2.EGF receptor: Gefitinib, Erlotinib, Cetuximab
3.Angiogenesis inhibitors: Bevacizumab Sunitinib
4.Proteasome inhibitor: Bortezomib
5.Unarmed monoclonal antibody: Rituximab,Trastuzumab

C. Hormonal drugs:
1.Glucocorticoids: Prednisolone and others
2.Estrogen: Fosfestrol, Ethinylestradiol
3.Selective estrogen receptor modulators: Tamoxifen, Toremifene
4.Selective estrogen receptor down regulators: Fulvestrant .
5.Aromataseinhibitors:Anastrozole ,Letrozole,Exemestane
6.Antiandrogen: Flutamide, Bicalutamide
7.5-α reductase inhibitor:Finasteride ,Dutasteride
8.GnRH analogues Nafarelin, Leuprorelin Triptorelin
9.Progestins: Hydroxyprogesterone acetate.[3]

Invitro Methods:

Tetrazolium Salt Assay:
This colorimetric assay assesses the viability, proliferation, and activation of cells in a sensitive, accurate manner.The assay relies on mitochondrial dehydrogenase enzymes ability to change the yellow, liquid substrate 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl azo dye bromide (MTT) into a dark blue, water-insoluble formazan product. The number of cells in a range or cell lines directly correlates with the quantity of formazan generated.

Method:
To ascertain the enzymatic characteristics, it is carried out. Trypsinized cells from certain cell lines in the log phase of growth are counted in a hemocytometer, adjusted to the proper density, and incubated with 384-well plate (96 well plates) The cells are given different medication concentrations for a predetermined amount of time. After each well has been filled with MTT dye, the plates are placed in a Humidified incubator and maintained at 37 degrees Celsius for four hours.The plates are removed from the incubator, and at room temperature, dark-blue formazan crystal is fully dissolved in DMSO and isopropanol. The samples are then examined at 570 nm by an ELISA reader. Calculated is the percent cell viability compared to the control.

Sulforhodmine b Colorimetric Assay:

Principle:
Capacity of SRB to bind to proteins in cells that have been TCA-fixed to tissue culture plates. Hot pink aminoxanthine color with two sulfonic groups is known as SRB. Sulfate reduction binding is stoichiometric. The Sulphorhodamine B assay assesses the quantity of whole-culture proteins, which should be proportionate to the number of cells. Amount of dye recovered form cells were stained proportionate to the cell mass. Sulphorhodamine B, a proteins staining dye, is used to

stain cell culture. The free dye is then washed away using acetic acid. The quantity of SRB adsorption is inversely associated with the rate of live cells that remain in a culture following drug treatment when dead cells ultimately lysis or are lost throughout the procedure.

In Vivo Methods:

Chemical Carcinogen Model:

Mouse skin papillomas caused by DMBA 2-stage experimental carcinogenesis > Launcher - DMBA(dimethylbenzanthracene), TPA (12-0-tetradecanoyl-phorbol-13acetate) is a potent promoter. Mice were given a single dosage of 2.5 mg of DMBA and 0.2 ml of acetone containing 5 to 10 ug of TPA twice a week. At 8 to 10 weeks, papilloma symptoms start to manifest.

Comparing the treatment group's tumour incidence and occurrence to the DMBA control group.

Method:

Mice get a single injection of 2.5 ug of DMBA in acetone and then twice weekly applications of 5-10 ug of Rtp in 0.2ml of acetone beginning one week following the DMBA treatment. Incidence of tumours as a percentage and the number of treatment groups are contrasted with the DMBA control group. The drug being tested may be delivered orally or topically. In this model, DMBA controls often have a tumour incidence of 100%.It has also been demonstrated that repeatedly applying DMBA alone can promote carcinogenesis. Drug effectiveness is determined by the percent reduction in cancer incidence when compared to the incidence under carcinogen control.MNU Induced Rat Mammary Gland CA MNU causes cancers that are hormone dependent. 50-day-old Sprague-Dawley rats were given a single intravenous dose of methyl nitrosourea (MNU) at a rate of 50 mg/kg. In 75 to 95% of instances, adenocarcinoma will develop within180 days of the post-carcinogen. Drug efficacy is assessed; nevertheless, it is impossible to determine suppression of carcinogen activation. [5]

Animal cell culture technique theory:

Introduction:-

Animal tissue culture technology is now becoming a significant model for many scientists in various fields of biology and medicine. Despite the various developments in animal cell and tissue culture since the late 1800s, until the early 1950s progress in animal tissue culture was stalled due to the non-availability of a suitable cell line. Animal cell culture is a significant toolfor biological research. The importance of cell culture technology in biological science was realized a long time ago. Earlier dedifferentiation based experiments of cells due to selective overgrowth of fibroblasts resulted in the enhancement of culture techniques. The source of the isolated cells is usually an in vivo environment, but sometimes cells are also derived from an existing cell line or cell strain. Animal cell culture offers suitable model systems for investigating the following factors:

Drug screening and development.
Mutagenesis and carcinogenesis.
Normal physiology and biochemistry of cells.
Potential effects of drugs and toxic compounds on the cells.[6]

Biology of cultured cell:

The validity of the cultured cell as a model of physiological function in vivo has frequently been criticized. Often, the cell does not express the correct in vivo phenotype because the cell's microenvironment has changed. Cell–cell and cell–matrix interactions are reduced because the cells lack the heterogeneity and three-dimensional architecture found in vivo, and many hormonal and nutritional stimuli are absent. This creates an environment that favors the spreading, migration, and proliferation of unspecialized progenitor cells, rather than theexpression of differentiated functions.[7]

Aseptic techniques for animal cell culture:

Successful cell culture depends heavily on keeping the cells free from contamination by microorganisms such as bacterial, fungi, and viruses. Non-sterile supplies, media, and reagents, airborne particles laden with microorganisms, unclean incubators, and dirty work surfaces are all sources of biological contamination. Aseptic technique, designed to provide a barrier between the microorganisms in the environment and the sterile cell culture, depends upon a set of procedures to reduce the probability of contamination from these sources. The elements of aseptic technique are a sterile work area, good personal hygiene, sterile reagents and media, and sterile handling. Sterile Work Area The simplest and most economical way to reduce contamination from airborne particles and aerosols (e.g., dust, spores, shed skin, sneezing) is to use a cell culture .Good Personal Hygiene Wash your hands before and after working with cell cultures. In addition to protecting you from hazardous materials, wearing personal protective equipment also reduces the probability of contamination from shed skin as well as dirt and dust from your clothes. Sterile Reagents and Media Commercial reagents and media undergo strict quality control to ensure their sterility, but they can become contaminated whilehandling.[8]

Safety Protocol for animal cell culture:-

When working with potentially hazardous material, it is important to be aware of the possible risks associated with both the material and the experimental protocol. All cell cultures are considered a biohazard because of their potential to harbor an infectious agent.
The degree of hazard depends on the cells being used and the experimental protocol. Primary cell cultures in particular should be handled carefully as these cultures have a high risk of containing undetected viruses. Although commonly used cell lines are generally assumed to be free of infectious agents, care should still be exercised when working with these cell lines as it is possible that they contain infectious agents, such as latent viruses.[9]

Application of cell culture techniques in drug discovery / evaluation:-

It is also used in drug screening and development and large scale manufacturing of biological compounds (e.g. vaccines, therapeutic proteins). The major advantage of using cell culture for any of these applications is the consistency and reproducibility of results that can be obtained from using a batch of clonal cells.
Model System: Cell culture are used as model system to study basic cell biology and biochemistry, to study the interaction between cell and disease causing agents like bacteria, virus, to study the effect of drugs, to study the process of aging and also it is used to study triggers for ageing.
Cancer Research: The basic difference between normal cell and cancer cell can be studied using animal cell culture technique, as both cells can be cultured in laboratory. Normal cells can be converted into cancer cells by using radiation, chemicals and viruses.
Replacement Tissue or Organ: Animal cell culture can be used as replacement tissue or organs. For example artificial skin can be produced using this technique to treat patients with burns and ulcers.
Gene Therapy: Cultured animal cells can be genetically altered and can be used in gene therapy technique. First cells are removed from the patient lacking a functional gene or missing a functional gene. These genes are replaced by functional genes and altered cells are culture and grown in laboratory condition.[10]

Animal Cell Culture Techniques:

Bladder cancer

Any of the several cancers that develope in the cells of the bladder. Blood in the pee, urinating pain, and low back discomfort are all symptoms. It is brought on when the bladder's lining epithelial cells develop into cancer. Smoking, a family history of the disease, radiation therapy in the past, recurrent urinary tract infections and exposure to specific chemicals are all major risk factor for bladder cancer. Carcinoma is the most typical kind. Squamous cell carcinoma and adenocarcinoma are further kinds. The usual method of diagnosis is pseudocysts with tissue biopsies. Medical imaging and transurethral resection are used to stage the malignancy.

HTB-4
Product category Human cells **Organism** Homo sapiens, human**Morphology** Epithelial
Tissue Urinary bladder
Disease Transitional Cell Carcinoma
Applications 3D cell culture; Cancer research

Outcomes:

After the completion of report on DRUG EVALUATION METHOD I understood
Safety of drug is improved.
Medication misadventure including adverse drug events are avoided.
We reduced variation standardize therapy.
Therapy is optimized.[4]

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