DRUGS
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It would be proper to review the biological activity of some of the drugs that have been used in various studies so far including those in the present study.

Lincomycin

Lincomycin is an antibiotic elaborated by an actinomycete, *Streptomyces lincolnensis*. Lincomycin is a derivative of the aminocarboxylic acid, L-4-n-propylglycinic acid, attached to a derivative of an arctose plus a sulfur atom.

Concentrations of Lincomycin of less than 0.5 microgram/ml inhibit the multiplication in vitro of *K. pneumoniae*, Group A strep. *pyogenes*, Strep. *viridans* and *B. anthracis*. *C. diphtheriae*, *C. tetani* and *C. perfringens* are suppressed by concentrations lower than 2 microgram/ml. Susceptibility of *Staph. aureus* to drug is variable; while most strains are sensitive to about 2 microgram/ml, about 15% of strains grow in a concentration of 5 microgram/ml. The antibiotic is highly active against most types of *Bacteroides* and other anaerobes. Lincomycin is not inhibitory for most strains of *N. gonorrhoeae*, *N. influenzae* and *Enterococci*, *Gram negative Cocci*, *viruses* and *fungi* are resistant.

Lincomycin binds exclusively to the 50 S subunits of ribosomes and suppresses the bacterial protein formation by inhibiting peptide bond synthesis. Erythromycin
can reverse the inhibition produced by lincomycin probably reacting on the same site of ribosome, the activity of lincomycin is blocked even if bacterium is sensitive to it.

Lincomycin is rapidly but partially absorbed from gastrointestinal tract. Peak plasma concentrations average about 255 microgram/ml after an oral dose of 500 mg and detectable antibacterial activity persists for 12 hours or more.

Intramuscular injection results in maximal plasma level within 30 minutes. With 600 mg intramuscularly every 12 hours, maximal plasma levels are 15-20 microgram/ml. Intravenous infusion over a 2 hours period of 600 mg of drug produces concentrations in therapeutic range for 14 hours. The biological half life after oral, intramuscular, or intravenous administration is about 3-6 hours. In patients with hepatic insufficiency half life of drug is most doubled, even when renal function is normal.

Lincomycin is distributed in both extracellular and intracellular fluids and is detectable in most human tissues.

Oral administration of lincomycin can cause glossitis, stomatitis, nausea, vomiting, enterocolitis, pruritis ani, vaginitis, urticaria. Parenteral administration has been followed rarely by neutropenia, leukopenia and thrombopenia all of which disappear when therapy is stopped. Elevation of serum Glutamic Oxaloacetate trans-
aminase have occasionally been observed after Lincomycin, but in some cases there is a false reaction.

Lincomycin hydrochloride, U.S.P. (Lincocin) is available in tablets and capsules containing 250 to 500mg and as a sterile solution (300 mg/ml) for parenteral use.

(Goodman and Gilman)

Kanamycin

Kanamycin is an antibiotic produced by Streptomyces kanamyceticus. Kanamycin is a polybasic water soluble substance. It contains two aminosugars linked glycosidically to 2 deoxysterptamine. Kanamycin resembles neomycin and has some chemical similarity to Streptomycin.

Kanamycin has a broad range of activity against Gram positive and Gram negative microorganisms. Sensitive bacteria include E. coli, A aerogenes, K. Pneumonise, proteus species the paracolon group, Salmonella, Shigella, Vibrio, Neisseria, Brucella, M. tuberculosis, atypical mycobacteria and staph. aureus. Resistant Micro-organisms include pseudomonas, enterococci, Bacteroides, Clostridia and other anaerobes, strep. viridans, coxsidioide, Yeast and fungi. The levels of kanamycin required to produce bacteriostatic and bactericidal effects are not greatly different. As kanamycin has been used more extensively resistant strains of stapy. aureus (up to 30% in some hospitals) K. Pneumonise, Proteus, Aerobacter, E. coli Salmonella, Shigella and
Paracolon group have been isolated from infected patients.

Kanamycin is poorly absorbed from the gastrointestinal tract, and most of an ingested dose is eliminated in the faeces, very low plasma concentrations are detectable, after oral medication in some individuals. Intramuscular injection of one gram of kanamycin yields a peak plasma level of 20–35 microgram/ml at about one hour; and falls to 1.2 microgram/ml or less at 12 hours. The level of kanamycin in blood is higher in older individuals. Excessive concentrations develop in patients with renal insufficiency. Kanamycin is not bound to plasma proteins. Repeated injections do not lead to accumulation in the blood if renal function is normal. Parenteral administration of kanamycin results in the appearance of appreciable concentrations of drug in pleural, ascitic, synovial, and peritoneal fluids. The antibiotic diffuses poorly into bile, faeces and amniotic and prostatic fluid.

Kanamycin sulfate, U.S.P. (KAMTRA), is available as an injectible solution in vials containing 500 milligram in a two ml. or 1.0 gm in a 3 ml volume, in paediatric vials (75 mg/2 ml), and for oral use in capsules containing 0.5gms.

Among the hypersensitivity reactions that have been noted in individuals receiving kanamycin parenterally are eosinophilia, fever, maculopapular rashes, pruritus and anaphylaxis. The most important side effects of kanamycin
stem from its ototoxicity and nephrotoxicity. Both the
cochlear and vestibular portions of the auditory nerve may
be damaged. Conversational hearing loss may be prevented
by omitting the drug as soon as any evidence of auditory
injury is manifest; this requires frequent audiometric
study. Neurotoxicity of kanamycin is a curare-like effect
on neuromuscular junctions. Paralysis of respiration
reversed by neostigmine may occur when the antibiotic is
instilled into the peritoneal cavity immediately after
abdominal surgery, especially when a neuromuscular blocking
drug has been administered.

**Gentamycin**

Gentamycin is a broad spectrum antibiotic derived
from Micromonospora purpurea. Gentamycin consists of
three closely related components - Gentamycins $C_1$, $C_2$ and
$C_{12}$ - with very similar molecular weights. Structural
formulas of the gentamycin components have not yet been
established. The drug is water soluble and stable to heat
and to a wide range of pH.

The three components of gentamycin have nearly
identical antimicrobial activity in vitro. Despite disper-
te reports, it is generally agreed that about 95% of pseud.
aeruginosa are inhibited by 10 microgram/ml or less of the
drug. E. coli, Klebsiella and aerobacter are also highly
sensitive. Practically all penicillin sensitive and some
methicillin resistant strains of staph. aureus are suppre-
ssed by a concentration of 5 microgram/ml or less. Group A streptococci, N. pneumoniae, past. malocida, N. influenzae, and bacteroids are reasonably sensitive to gentamicin. Mycobacterium tuberculosis and mycoplasma pneumoniae are highly sensitive. Neisseria gonorrhoea and N. meningitidis and corynebacteria are relatively resistant, the drug is bactericidal in concentrations 2-3 times those required to produce bacteriostasis.

Gentamicin is not absorbed to as significant degree from the gastrointestinal tract. Single oral dose upto 1.5 gram in man are absorbed only to the extent of about 0.2%. Intramuscular injection of gentamicin sulfate in a dose of 0.4 mg/kg produces a peak plasma level of about 1.5-3 microgram/ml at 1 hour. The half life of gentamicin is about 4 hours in individuals with essentially normal glomerular filtration rates; in patients with uraemia, the drug accumulates in body and its half life may be as long as 45 hours.

Approximately 30% of antibiotic is bound to plasma proteins. Gentamicin is excreted by glomerular filtration; little, if any, of the drug undergoes tubular secretions or reabsorption. Concentration of the gentamicin in urine may be 50-100 times higher than those simultaneously present in the blood. The drug diffuses into pleural and peritoneal fluid.
The official preparation is gentamycin sulfate, U.S.P. (garamycin sulfate). It is available in 2 ml vials containing sterile solution of 40 mg/ml.

Among the untoward reactions to gentamycin are nausea, vomiting, headache, transient proteinuria, elevation of blood urea, nitrogen, increase in serum transaminase and alkaline phosphatase, and transient macular skin eruptions. The most important untoward effect of gentamycin involves the VIIIth cranial nerve. Ototoxicity appears in about 1% patients, vestibular function is injured to a greater extent than hearing. It may be very severe, and function may be lost completely. Gentamycin should not be administered to pregnant women (Goodman and Gilman).

**Streptomycin**

Streptomycin is one of the aminoglycosidic antibiotics and is N-methyl-L-glucosaminidestreptosside-streptidine. The drug is made up of the three components streptidine, streptose, and N-methyl-L-glucosamine; streptomycin base and its inorganic acid salts are soluble in water. It remains stable in the dry state at room temperature for at least 1 year.

High concentrations of streptomycin are bactericidal whereas low concentrations are bacteriostatic in vitro. Very low concentrations of streptomycin may stimulate bacterial growth. The microorganisms that are sensitive to concentrations of streptomycin readily attainable in man
are Brucella, Erysipelothrix, Hemophilus ducreyi, listeria monocytogenes, Actinobacillus mallei, Nocardia, Pasteurella pestis and tularensis, many but not all strains of Mycobacterium tuberculosis and Shigella. The species with stains exhibiting a wide variation in susceptibility include Diplococcus pneumoniae, S. typhosa and other Salmonella, E. coli, H. influenzae, the gonococcus and the meningococcus, Proteus vulgaris, staphy. aureus and albus, Strepto. pyogenes Group A, strep. faecalis, strep. viridans, and vibrio comma. Bacteroides, Clostridium, Rickettsia, Candida, Histoplasma, and Entamoeba histolytica, Trichomonas vaginalis and all viruses are totally resistant to streptomycin.

Orally administered streptomycin is poorly absorbed from the gastrointestinal tract but is not inactivated therein. As a result, the enteric flora is markedly suppressed.

Streptomycin acts directly on the ribosome where it inhibits protein biosynthesis and decreases the fidelity of translation of the genetic code. A major disadvantage of streptomycin therapy is the development of bacterial resistance to the drug.

Very little streptomycin is absorbed from the intestinal tract. Instillation of 0.5 gm intrapleural results in rapid absorption of streptomycin into the blood.
Streptomycin is absorbed very well and rapidly from intra-
muscular and subcutaneous sites, and is distributed in
blood and plasma, and also in the extra cellular fluids.
It enters the peritoneal fluid readily from the circulation
plasma and peritoneal levels are about equal in the presence
of peritonitis.

Streptomycin is excreted by glomerular filtrat-
tion. The half life of antibiotic is 2-4 hours in normal
adults and increases to 100 hours when blood urea nitrogen
values are in the range of 100-150 mg/100 ml. Streptomycin
sulfate U.S.P. is supplied for parenteral injection in a
vial containing 1 or .5 grams of the base.

Side effects are hypersensitivity reactions,
drug fever and Labyrinthine damage (Goodman and Gilman).

Benzylpenicillin

Benzylpenicillin (penicillin G) is an unstable
acid but its sodium or potassium salt (soluble or crys-
lline penicillin) is stable when dry. It is readily soluble
in water but the solution is unstable, its activity being
slowly lost even at 4°C.

Because of its almost complete lack of toxicity
in patients who show no hypersensitivity to it, penicillin
can usually be given, if necessary, in very large doses.
It is active against almost all the Gram positive and
some of the gram negative organisms. Sensitive organisms include the streptococci, staphylococci, gonococci, pneumococci, meningococci, the spirochaetes, the actinomyces and the large viruses. In clinical terms this means that the range of conditions likely to respond to penicillin therapy includes wound sepsis, cellulitis, puerperal sepsis, bacterial endocarditis, pneumonia, syphilis, gonorrhoea and some infections of the skin, the eye and the throat. Penicillin may also be used to provide an antibiotic umbrella to prevent the accumulation of micro-organisms in the blood (bacteraemia) following the removal of infected teeth or tonsils from patients with valvular heart disease.

Some strains of some of the bacterial species listed as penicillin sensitive are resistant to the drug and their numbers have increased with the years as the sensitive strains have succumbed. This is particularly true of *Staphylococcus aureus*. Many resistant strains of gonococcus have also appeared.

**General Properties** - Benzylpenicillin is active when taken by mouth but no more than one-third of the amount ingested reaches the bloodstream and absorption is still further reduced if food is present in the stomach or duodenum. The unabsorbed penicillin is excreted in the faeces. Benzylpenicillin is unstable in acid and some destruction may take place in the stomach.
Lenzylpenicillin is absorbed largely from the duodenum. It is secreted by the renal tubules. Consequently it is very rapidly eliminated from the body and large and frequently repeated doses have to be given if an effective concentration of the antibiotic is to be maintained in the blood and tissues. Intramuscular injection provides the most useful mode of administration.

**Enzymatic Inactivation** - An enzyme, penicillinase, splits penicillin to give penicilloic acid. The ability to produce penicillinase is one of the reasons why an organism may not be sensitive to penicillin— the tubercle bacillus and resistant strains of *Staph. aureus*, for example are penicillinase producers. A mixed infection due to a number of bacterial species, only one of which produces penicillinase may be completely resistant to penicillin because the enzymes released by one species protects all the others.

**Hypersensitivity Reactions to Penicillin** - The reaction is an anaphylactic one reminiscent of serum sickness but it may appear in those who are apparently being exposed to the drug for the first time. In these instances it has to be assumed that the patient has become sensitized as a result of a previous contact of which he was unaware. One possibility is that he may have drunk milk from an animal which has itself received penicillin.

Anaphylactic responses to penicillin not infrequently have a fatal outcome. Penicillin may provoke re-
actions less violent than a fully blown anaphylaxis. The most common are skin rashes, they may appear in those who only handle the drug.

Skin testing has been recommended but some authorities claim that this method does not adequately identify hypersensitive individuals. Moreover, a few instances are known of patients in whom the skin testing procedures has itself precipitated a fatal anaphylaxis.

No twitnading their serious nature, anaphylactic responses represent anidiosynaratic reaction attributable more to the patient than to the drug.

High osmotic pressures develop in bacterial cells. The ingress of water, with consequent lysis is prevented by the cell wall, a substantial structure which forms up to one fifty of the dry weight of the cell. Penicillin interferes with the formation of the cell wall of the developing micro-organism and thus exposes it to the lytic action of any solution whose osmotic pressure is less than that of the cell's own contents.

Penicillin probably interferes with the synthesis or the activity of an enzyme that controls the incorporation of muramic acid peptides into the structure of the cell wall. The production of the peptides themselves may also be interfered with. (Lewis's).

**METRONIDAZOLE**

It is a potent amoebicide and is highly effective by mouth as well as parenterally (by intravenous infusion).
Apart from the *Entamoeba histolytica*, it is also effective against non-sporing anaerobes (bacteroides), *Trichomonas vaginalis* and *Giardia lamblia*.

![Chemical structure of metronidazole](image)

**Metronidazole**

Metronidazole is adequately and rapidly absorbed from the gut. It crosses the placental barrier and is present in milk. It is partly metabolized in the body and after large doses, the metabolites may impart a dark color to the urine.

The adverse reactions are mild and seldom necessitate discontinuation of therapy. Nausea, anorexia and metallic taste in the mouth are fairly common. The drug may produce an antabuse like reaction characterized by flushing, nausea and vomiting in some patients after the intake of alcohol.

The recommended dosage of metronidazole for *Amoebiasis* is 200 - 400 mg orally three times daily for 7-10 days. For anaerobic infections (bacteroides), it is given rectally as suppositories in the dose of 1 gm eight hourly if the patient is nil orally or 500 mg thrice daily as slow intravenous infusions and 200-400 mg three times daily by mouth (if patient is orally allowed) for 7-10 days.