FORMULATION OF VETERINARY DRUGS

Synonyms:

- Drug formulations
- Drug dosage forms
- Drug delivery systems
- Drug Preparations

Drug Formulations

- Pharmaceutical preparations of a drug.
- Compounded to provide convenient means of administering a dose of the drug.
- Provide accurate and reproducible dosage.
- May be designed for oral, parenteral or topical application.
- Entails mixing of active ingredient with a variety of excipients e.g starch (for tablets), lactose (for capsules or tablets), solvents (for liquids and injectables), preservatives, coloring agents etc.

Formulations and Drug Therapy

- Similar formulations containing the same amount of active compound do not necessarily elicit the same therapeutic response.
- Formulation processes influence the release rate of drug from dosage forms e.g high compression force increases hardiness (mechanical resistance) of tablets. This results in prolonged disintegration and dissolution rate.
- Changes in drug release rate from a formulation changes absorption rate, bioavailability and plasma concentration versus time profile (See Fig. I).

Parameters Used to Compare Drug Formulations

- Chemical equivalence: refers to identical dosage forms which contain identical amount of the same chemical substance and meet the physicochemical standard of the Pharmacopoeia.
- Biological equivalence: a condition attained when chemically equivalent dosage forms administered in the same amount provide the same biological or physiological availability which can be determined by measuring plasma or tissue levels of the drugs.

- Clinical equivalence: a condition attained when two chemically equivalent dosage forms administered in the same amount provide the same therapeutic effect as measured by the control of symptoms of a disease.

Factors influencing choice of Drug Formulation

- Nature of the disease (acute, chronic)
- Site of the disease (systemic, local)
- Physicochemical properties of the drug (volatile?)
- Chosen route of administration

Classes of Drug Formulations

1. Immediate release e.g tablets, ointments, aerosol etc
2. Controlled release e.g subdermal implants etc

Immediate Release Drug Formulations

Solid Dosage Forms:

Tablets

- A mixture of active drug and inert binding materials or excipients, usually in powder form, pressed or compacted into a solid.
- Some tablets are in the shape of capsules, and are called “caplets”

Wettable Powder

- Drug dosage form in fine particles.
- Could be sprinkled on feed or dissolved in drinking water.
- It is commonly used in poultry.

Suppository

- Inserted as a solid into the rectum (rectal suppository), vagina (vaginal suppository) or urethra (urethral suppository), where it dissolves inside the body to deliver the drug.
- Used to deliver both systemically-acting and locally-acting medications.

Capsule

- Hard gelatin e.g ampicillin capsule for dry, powdered ingredients or miniature pellets.
- Soft gelatin e.g garlic capsule.

- Primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Semi solid Dosage Forms:

- Examples are ointments, creams and gels commonly used to treat dermatological diseases.
- Ointments are homogeneous, viscous, semi-solid, greasy, thick oil, intended for external application to the skin or mucous membranes.

Liquid Dosage Forms:

Suspension

- Formulation of two-phase system composed of a finely divided solid that is dispersed in a liquid phase, which is usually water.
- Suspensions are common as oral drug preparations.
- **Never administer intravenously.**

Emulsion

- Aqueous suspension of insoluble liquid substance usually with emulsifying agent to stabilize the preparation.
- Usually administered orally or topically.

Solutions

- Oral Solution: Aqueous preparation of drug for oral use. The drug is in true solution.
- Parenteral Solution: Sterile and pyrogen free aqueous preparation for injection. Drugs may also be dissolved in oil for prolonged absorption.
- Ophthalmic Solution: Sterile hypotonic aqueous solution of drug for administration into the eye.

Tinctures

- Tinctures vary in strength. Examples are tincture of iodine, opium, belladonna and digitalis.

Liniment

- Liquid preparation of a drug in which the drug is dissolved or suspended in dilute alcohol or water. They often contain dissolved or emulsified oils and are applied to the skin by rubbing or massage.

Lotion

- Usually an oil in water base which contains insoluble medicinal agents in suspension and is applied to the skin without rubbing following which the solvent evaporates leaving a film of drug.

Aerosol

- The drug exists as liquid or solid particles so small as to remain suspended in air for long periods.
- Aerosol generators may produce particles in 1-5μm ranges.
- For therapeutic purpose, aerosols are introduced in the body by inhalation.

Controlled-Release Drug Delivery Systems

Synonyms: Sustained; Modified; Prolonged; Slow; Gradual and Extended Forms

- Provide an initial therapeutic dose immediately following administration and subsequently followed by a gradual release of the drug over a prolonged period of time.
- Extend the duration of pharmacological response compared to the conventional single dose formulation.
- They produce therapeutic blood level quickly and maintain such levels without the usual "peak –and-valley" effect of a normal dosage form.
- Examples: enteric coated tablets, sub dermal implants, depot antibiotics etc.

Advantages:

- prolonged absorption
- reduced peak blood concentration so side effects associated with peak blood levels are minimized
- predictable and reproducible drug release kinetics
- premature inactivation and elimination of the drug is avoided
- extended and regular pattern of therapeutic effects

- extended duration of drug action
- reduced frequency of drug administration and animals restraint
- improve compliance
- targeting of drugs to specific sites and selectivity of action is possible

Disadvantages:

- Toxicity may result if actual release rate becomes high (large doses are given at once, it being assumed that there will be slow but continuous release of drug from the formulations).
- A reduction in the expected rate of release may result in therapeutic failure.

Fig I: Plasma Concentration/Time Profile

- The figure is a simulated plasma concentration versus time curve.
- Obtained following a single oral administration of three chemically equivalent formulations I, II, and III.
- Formulations have different release rate (I>II>III).
- Formulation I has a rapid onset of activity, higher magnitude of response and a shorter duration of action compared to II.
- The drug release rate from formulation I is such that the plasma concentration exceeds the maximum safe concentration (MSC). Thus, some toxic side effects will be observed.
- Formulation III is therapeutically non-effective since the minimum effective concentration is not attained.

DRUG PRESCRIPTION ORDER

Instructural Objectives:

- Introduction
- Metrology in Prescription
- Prescription Order Writing

Prescription Order-Definition

- A written instruction by a veterinarian to a pharmacist for issuing medical preparations for a patient.

- It primarily states what is to be given; to which animal; how much; how often; which route; how long; and by who?
- It is a legal document.

Prescription Writing in Vet Practice

- Veterinarians seem to be more adept at dispensing rather than prescribing drugs.
- Level of veterinary practice is such that the practicing vet depends on profit from the dispensing and sale of drugs.

Reasons Why Veterinarians Should be Proficient In Writing Prescription Order

- The vet can charge just about the same fee as when drugs are dispensed.
- Writing a prescription reduces the investment tied up in drug inventory.
- Prescribing provides the vet with a supply of pharmaceuticals that might not always be available on the shelf of the clinic.
- If a client does not pay his/her bills, the cost of the medicines prescribed is not lost.
- Clients are more likely to pay for two smaller fees than one large fee.

Types of Prescription Order

Pre-compounded:

- Prescription of drugs in fixed dose combinations prepared by pharmaceutical industries.
- Dispensed without further alterations.
- Simple but drug dosage cannot be manoeuvered to suit clinical conditions.
- Now used commonly.

Extenporaneous or compounded:

- The Veterinarian selects drugs, their doses and formulations to be made and then instructs the pharmacist to compound the medicine.
- Selections and doses can be made to suit clinical conditions.
- Not common nowadays.

What To Avoid in Prescribing Drugs

- Prescribing a drug without demonstrated efficacy.
- Prescribing a drug with inherent hazard that is not justified by the seriousness of

the disease. This is sometimes referred to as 'heroic' measures.

- Prescribing drugs in inadequate amounts and for inadequate periods.
- Simultaneous use of more than one drug without consideration for interaction.
- Prescribing drugs without consideration for cumulative effect.
- Prescribing of needlessly expensive drug.

PRESCRIPTION ORDER WRITING

Rules of Prescription Writing

- Language of the prescription is English with some Latin abbreviations.
- The use of Latin phrases has become obsolete.
- Official/Generic names of drugs are preferred.
- Trade or proprietary names may be used but these restrict the pharmacist who must supplies the drug to the specified name.
- Substitution of one therapeutic agent for another is not permitted even if the two drugs are considered pharmacodynamically equivalent e.g $NaHCO_3$ for Mg trisilicate.
- If the vet prefers a particular product but is unsure of its availability, he/she could insert the trade name in bracket after the official name e.g acetylsalicylic acid (Bufferin®).
- Write "Brand Necessary" on the prescription if you insist on the particular product.

Metrology in Prescription

- Metrology is the study of weights and measures.
- The metric system is used exclusively now in expressing drug weights.
- Drug weights are measured most commonly in milligrams.
- Dosages are expressed as x mg of drug A per kg of body weight of animals.
- Concentrations of liquid preparations are expressed as x mg of drug A per ml.
- Dosages of drug administered in feed or water may be expressed as parts per million (ppm).

Parts of A Prescription Order

Superscription:

- Practice name and address: This may appear before or after the prescription.
- Date of prescription: This is essential for record purposes and it also enables the pharmacist to detect submission of old prescription order.
- Name and address of the client
- Identification of the animal
- The symbol, partly from the Latin word ‘recipe’ meaning ‘take thou’

Inscription:

- Drug Name
- Dose=Quantity of drug per dose form
- Dose Form = The physical entity needed, i.e tablet, suspension, capsule
- Clarity of number - 0.2, 20 not 2.0 (zeros lead but do not follow)

Subscription:

- This is the doctor’s instruction to the pharmacist as to what the pharmacist is to do with the ingredients i.e
- the type of pharmaceutical preparation to be made
- the quantity or number of packs to be dispensed.

Signature or Transcription:

- This is the directive to the pharmacist as to what details should appear on the label as directive to the animal owner or patient (in human medicine).
- The instructions contained in the signature usually encompass the amount of drug to be taken, the frequency of the dose, route of administration and other factors.
- It is linked to the Latin word ‘sigma’ meaning ‘write’, ‘mark’ or ‘label’.

Refill information

Prescriber’s signature and qualification.

Inscription protocol

- Avoid abbreviation
- Write the name of each drug on a separate line
- Capitalize the first letter in the name of each drug or ingredient

Subscription protocol

Subscription is usually a short sentence e.g

- Make a solution
- Mix and place in 10 capsules
- Dispense 10 tablets

Subscription could also be a word e.g "Mix" which may be written as 'M' an abbreviation from the Latin word ',misce' meaning mix.

Signature or Transcription Protocol

- The directives are preceded by the abbreviation 'Sig' or 'S' 'Label' e.g
  Sig. For animal treatment only. Apply calamine lotion daily to skin lesions on horse No MNO 734.
- The signature is usually written in English but several Latin phrases and abbreviations are inserted.
- The pharmacist usually translates these abbreviations and label the client's medicine accordingly e.g 1 cap tid, pc. Meaning 1 capsule 3 times daily after meals.
- Express dosages as mg/kg and the frequency of administration in hours such as q4h (every four hours) rather than tid.

write

- 'take' for those preparations designed for internal use
- 'apply' for ointment or lotion
- ínsert' for suppositories
- 'place' for drops.
- Never write "take as directed' i.e do not give a verbal directive.
- The intended purpose of the prescription can be stated e.g 'for relief of pain' Doing so reduces chances of errors.

The label should also contain

- The drug(s) and strength
- Special instructions (shake well, refrigerate etc).
- Warnings

ORGANIZATION AND MANAGEMENT OF A VETERINARY PHARMACY

Objectives:

- Maintain a permanent stock of drugs and appropriate medical supplies.
- Reduce costs of procurement and manage wastage.
- Save time and optimize the work of the members of staff.
- Easier to continuously evaluate consumption of drugs and medicaments.

Choice of drugs:

- Use the National Essential Drug List (drugs selected based on national requirements and drug policy).
- Medical items (materials for sterilization, injection, suture) should also be limited to the essentials and a standard list prepared.

Advantages of using the Essential Drug List

- Better therapeutic management due to more rational and safer use of a restricted number of essential drugs.
- Economic and administrative improvement at the level of purchase, storage, distribution and control.

Designation of drugs

- Use International Nonproprietary Name/Generic Name (INN) as exist in all standard lists.

Classification of drugs

Pharmaco-therapeutic classification:

- Drugs are grouped according to their therapeutic action.
- In some cases, a drug can appear in several groups.
- Easier to insert supplies from different origins as well as find a substitute for a missing product.

Alphabetical classification according to routes of administration:

Drugs are divided into four groups namely

- Oral drugs
- Injectables
- Infusion solutions stored separately because of their bulk
- Drugs for external use and disinfectants
- Smaller medical materials classified in sub-categories: dressing, injection, suture.

Drugs are then listed in alphabetical order within each group.

- This satisfies the criteria of simplicity and standardization needed for the whole management system.

- Non specialized personnel can work with it.

Note:

- Use whichever classification is adopted at every level of the management system (ordering, storage, distribution, dispensing) in order to facilitate all these procedures.

ARRANGEMENT OF MEDICINES AND MATERIALS

- Arrange stock according to the classification adopted.
- Every product should have its own well defined place shown by a large label giving the name of the product in INN, its form and dose; for example; Ampicillin caps 250mg.
- Narcotic drugs such as fentanyl, pethidine, morphine should be kept in a locked cupboard.
- Label the box and bottle of every drug correctly and clearly with the name of the product in INN, the dose, the form, the expiry date.
- Arrange the products with the ones with the latest expiry date at the back of the shelves and those that should be used first in the front.
- This arrangement is essential to avoid products extending pass their expiry dates and becoming unusable.

Storing bulky material

- Put a few boxes in their normal place and, on the label, state where the rest of the stock is kept.
- Do not separate the rest of the stock in several places.

Storing medical materials

Because of the diversity of the articles to be stored;

- It is preferable not to use a strict alphabetical ordering.
- Group the articles by category e.g injection material, dressing, sutures.
- Allow enough space for each drug
- The arrangement should make it possible to work “by sight”.

- It should be possible to pick out the number of boxes of each product.
- In a few minutes, it should be possible to work out how many weeks or months stock of a given product remains.
- An empty space behind a label immediately shows that the product is out of stock
- A few hours should be enough to do a complete stock inventory

A list of the commercial names and the corresponding INN can be put up

- to enable a person who is not familiar with the INN system to find their way around in times of emergency
- in case of sudden replacement
- in order to train the auxiliary staff

Management of the Pharmacy

Stock-control

Stock Cards - 1

- Main instrument for stock-control.
- For each item (drug and material), a stock-card is made out and regularly updated, preferably by the same person.
- These cards allow

- the identification of all movements of stock, in or out
- the theoretical stock level to be available at any time
- the consumption of the different users to be monitored
- the orders to be correctly foreseen
- an assessment of what and how much has been lost (difference between the theoretical stock and the actual stock after inventory)

Stock Cards -2

The following can be noted on the stock-card

- The name of the product in INN, the form and the dose
- All the movements (entries, exits, origin, destination) and the date
- Orders made and the date
- Inventories and the date
- Safety stock

- Maximum stock
- Other storage areas for this product
- Unit price
- The quantities are always recorded in units (e.g 5,000 tablets, 80 ampoules) and never by box (10 boxes of ampicillin tablets could corresponds to 200 tablets (10 boxes of 20 tablets) or 10,000 tablets (10 boxes of 1,000 tablets).

Stock Cards – 3

- Write only one movement on each line, even if several operations take place the same day.
- When an order is made, the date, supplier, and amount ordered are recorded. The stock column is not changed. When the order arrives, the amount received is included in the "incoming" column, and the "stock" column is then modified.

Calculations of Stock Levels

Monthly consumption:

- Calculated from the exit recorded on the stock cards.
- Add the quantities in the outgoing column from several months (3, 6 or 12) and divide the total by the number of months.

Working stock:

- Working stock corresponds to the amount of each drug consumed between supplies.
- For example, if the supplies arrive every three months, working stock = monthly consumptions x 3.

Safety stock (or reserve stock):

- This is the quantity below which the stock should never fall at the risk of running out of stock. This stock is planned to compensate for any delays in delivery, increases in consumption or possible losses.
- It depends on the delivery time of the orders.
- The quantity to be kept as a safety stock is generally calculated as half of the consumption during the time between two deliveries.

- It considers the risks of running out of stock and having drugs pass their expiry date that the pharmacy is able to take depending on factors such as resources and seasonal supply problems.

Quantity to order:

- The amount to order is based on

- stock according to the inventory when the order is made
- safety stock
- working stock

Order = (working stock + safety stock)- remaining stock on the day the order was made.

Inventory

- At least once a year, but if possible before every order, an inventory of the quantities actually in stock and their expiry dates should be made.
- The stock cards give a theoretical figure for the stock, but the quantities actually available should be checked product by product.
- Differences can arise through theft or errors in the record-keeping. These differences should be thoroughly investigated.
- An inventory can be made easily in a correctly arranged pharmacy.
- During the inventory, there should not be movement of stock.

PRESERVATION AND QUALITY OF THE DRUGS

- For an effective treatment, it is vital to maintain the quality of the drugs, which means that their identity, dosage and condition have to be assured.
- Storage and climatic conditions (temperature, humidity and light) may affect drug quality.
- Drugs do not lose their efficacy suddenly at the expiry date. The deterioration rate process is very slow and varies widely.
- A product may come in various forms with varying deterioration rate.

Drug Quality

To obtain good quality drugs, try to acquire them in the best possible manner by

- dealing with reliable suppliers.
- assure quality maintenance through optimum transport and storage conditions.
- Choice of a supplier should never depend exclusively upon price.

Identification

- All drugs should be easily identifiable, both by the medical staff and the patient (client).
- In whatever form the drug is packed (bottle, bag or box), it must bear not only the name of the product inside, but also its dose and expiry date.
- Different products often look alike, or on the other hand, the same products may exist in different colours and/or form (e.g tablets or capsules).

Stability and Storage – Temperature

- Temperature, air and light influence the storage of drugs
- Standard storage temperatures:

Deep freeze - -15 to O^{o}C

Refrigerator - 0 to + 6^{o}C

Cooled - +6 to +15^{o}C

Room temperature - +15 to +30^{o}C

- Temperatures during transit and transport reach 56^{o}C to 60^{o}C in vehicles, or on loading platforms.
- This means that very often, the original expiry dates cannot be guaranteed.
- Freezing can cause precipitation of the active ingredients in solutions or break the ampoules.

Stability and Storage – Air

- Drugs may also be damaged by the influence of humidity and oxygen
- Therefore all drug containers must remain closed
- Special medical packing often opaque and waterproof, offers protection against the influences of air and light.
- Avoid repackaging, until first distribution

Stability and Storage – Light

- Excessive light may also harm drugs
- Solutions are particularly sensitive to light
- Injectable preparations have to be kept in the dark in their original packing
- Certain types of coloured glass give the misleading impression that they protect drugs from light.

Expiry date

- Packaging should bear the expiry date and any specifications as to storage conditions.
  - ➢ Minimum period is usually between 3 and 5 years.
  - ➢ Common antibiotics, hormone preparations, vitamins and liquid drugs in general will last 3 years from the date of manufacture.
  - Other sophisticated products have only a 1 to 2 year period before they expire.
  - These specs do not apply to products that have to be stored under special conditions (refrigerated).
  - Disposable materials in sterilized packs may be used as long as the packaging remains intact.

Deterioration

- to detect any changes as soon as they occur it is essential to be well acquainted with the normal characteristics of every drug (colour, smell, solubility, appearance).
- certain processes may however occur without any detectable change in the appearance of the products.

Consequences of Deterioration

- Antibiotics that have expired, and become less active, may encourage resistant strains.
- Changes may result in the formation of dangerous substances and increase in toxicity e.g tetracycline would be dangerous to use when it has become brownish and viscous even before the expiry date is reached.

- Drugs which lose their effectiveness may cause increased allergic reactions e.g penicillin and cephalosporin.

Dealing with Deteriorated Drugs

- Any loss in effectiveness should not be compensated for by administering higher doses, since this may lead to serious risks of overdosage.
- Do not use suppository, creams or ointments that have melted because of the heat. The active substance will no longer be homogeneously mixed.

Dealing with Expired Drugs

- Because of our tropical environment and the lack of adequate infrastructure to store drugs properly, the use of expired drugs must be avoided.
- Incinerate expired drugs and bury residual materials at a great depth, far away from any well or water reservoir.
- Keep a special spot for this operation

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COMPILED BY DRS O.T. ADENUBI AND K.T. BIOBAKU