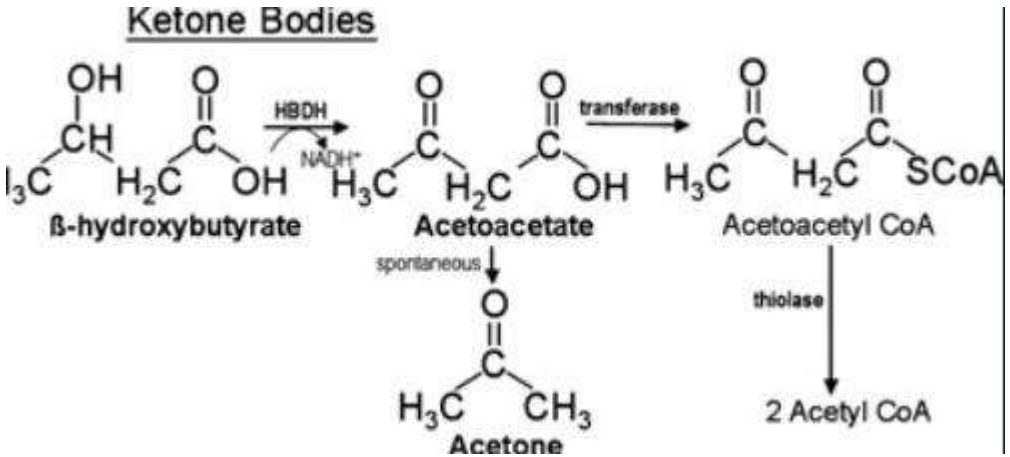
Metabolic Diseases of Importance in Domestic Animals

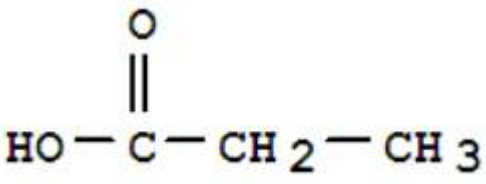
Dr. Abdul Samad

Lecture Plan

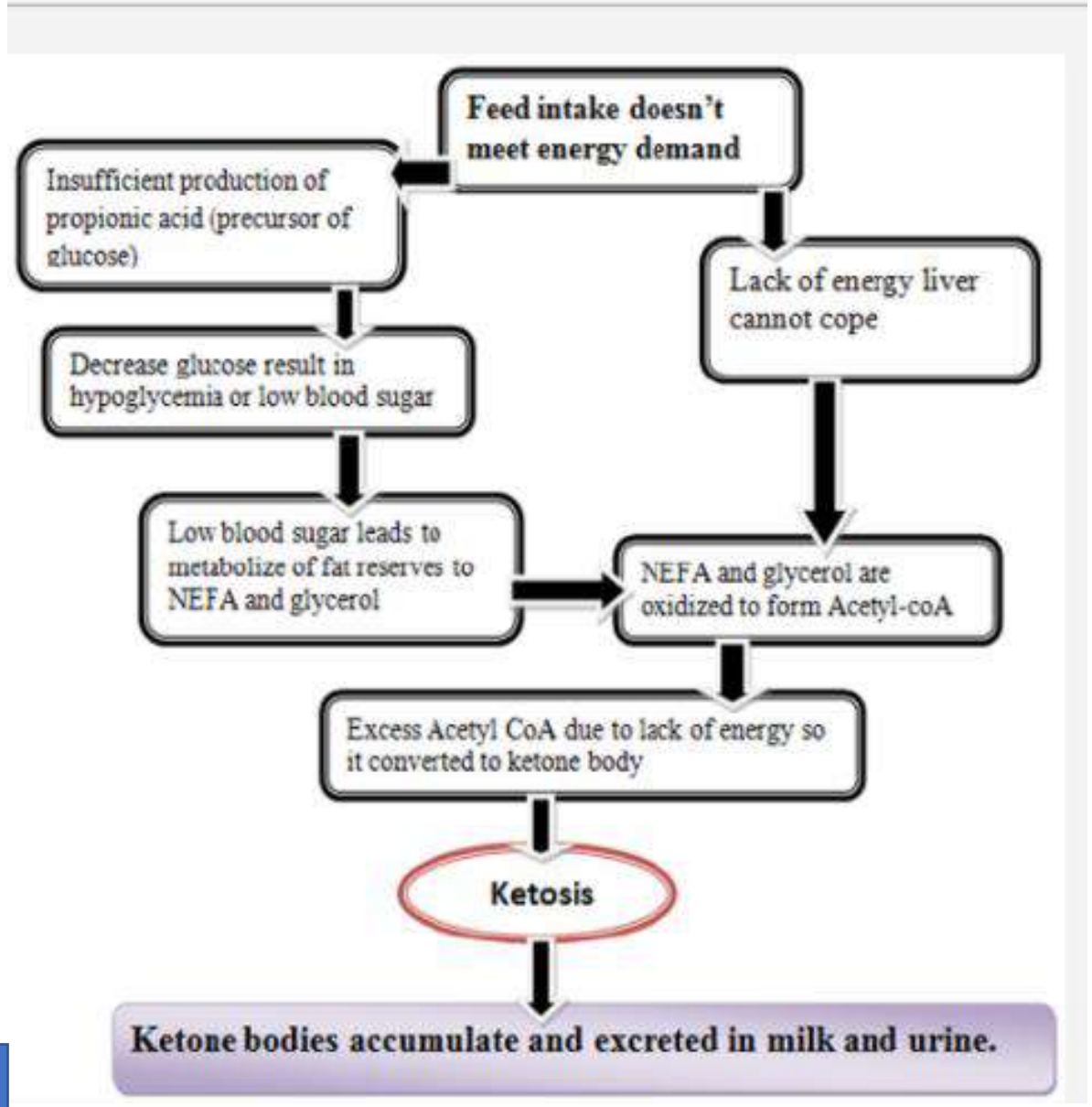
- Ketosis
- Phosphorus Deficiency / Hypophosphatemia
- Milk Fever

Biochemical Basis of Ketosis in Dairy Cows



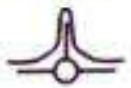
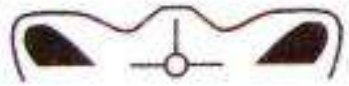
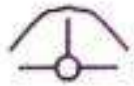
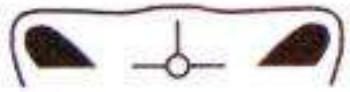
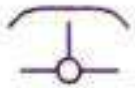
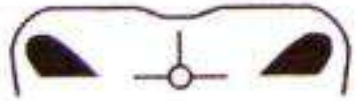
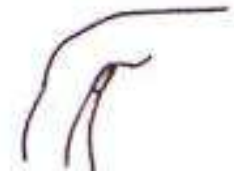


Propionate

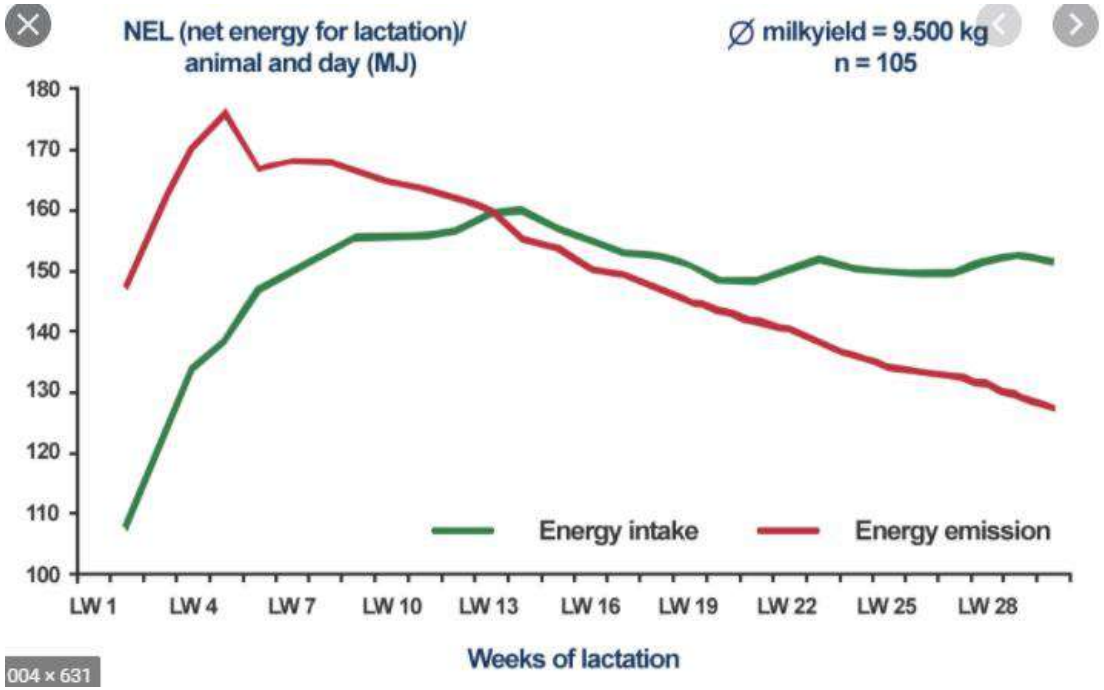


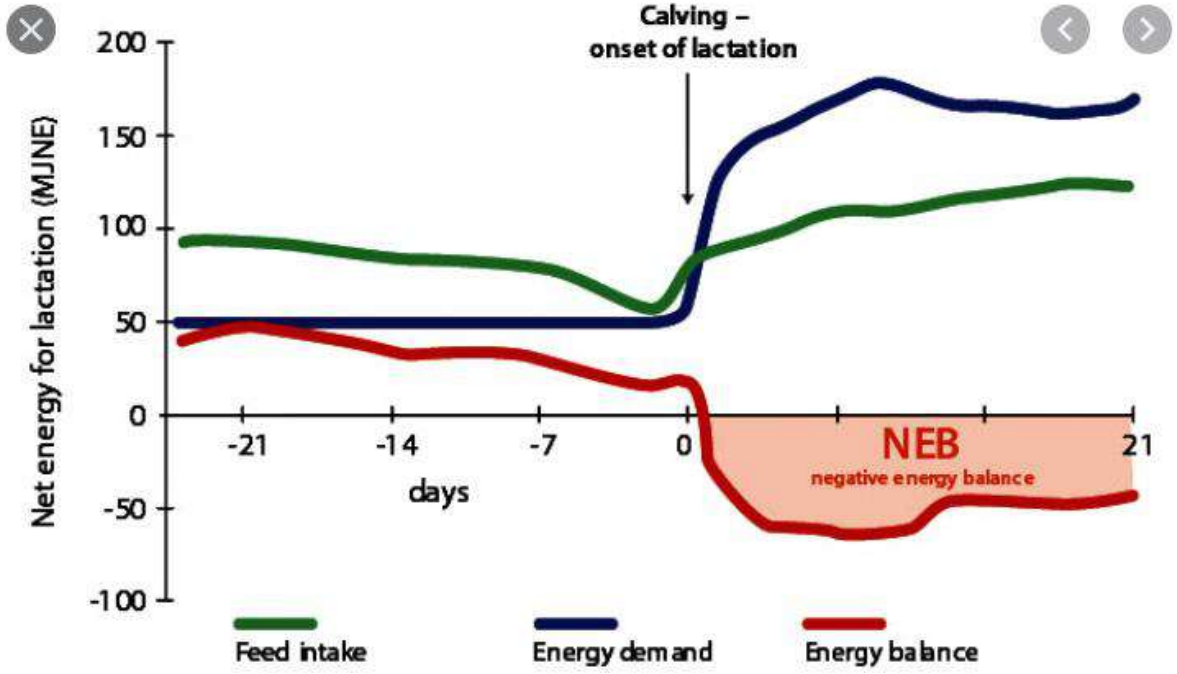
Ketosis- An Energy-Deficiency –associated Disease

- **Type I ketosis:** Ketosis cases occurring closer to peak milk production (21-50 days), low blood glucose
- Usually occurs at 4–6 week postpartum
  - More closely associated with underfed cattle experiencing a metabolic shortage of gluconeogenic precursors than with excessive fat mobilization.
- **Type II ketosis:** Occurs immediate postpartum (5-21 days)- in very early lactation- associated with fatty liver. When cows at calving have BCS > 3.75, high blood glucose, insulin resistance, low blood insulin levels
- Intense fat mobilization in cattle and hepatic deposition
- Immune function is disturbed- more prone for mastitis

Body Condition Score	Vertebrae at the middle of the back	Rear view (cross-section) of the hook bones	Side view of the line between the hook and pinbones	Cavity between tailhead and pinbone	
				Rear view	Angled view
1 Severe uncerconditioning					
2 Frame obvious					
3 Frame end covering well balanced					
4 Frame not as visible as covering					
5 Severe overconditioning					

Energy-Related Metabolic Disorder





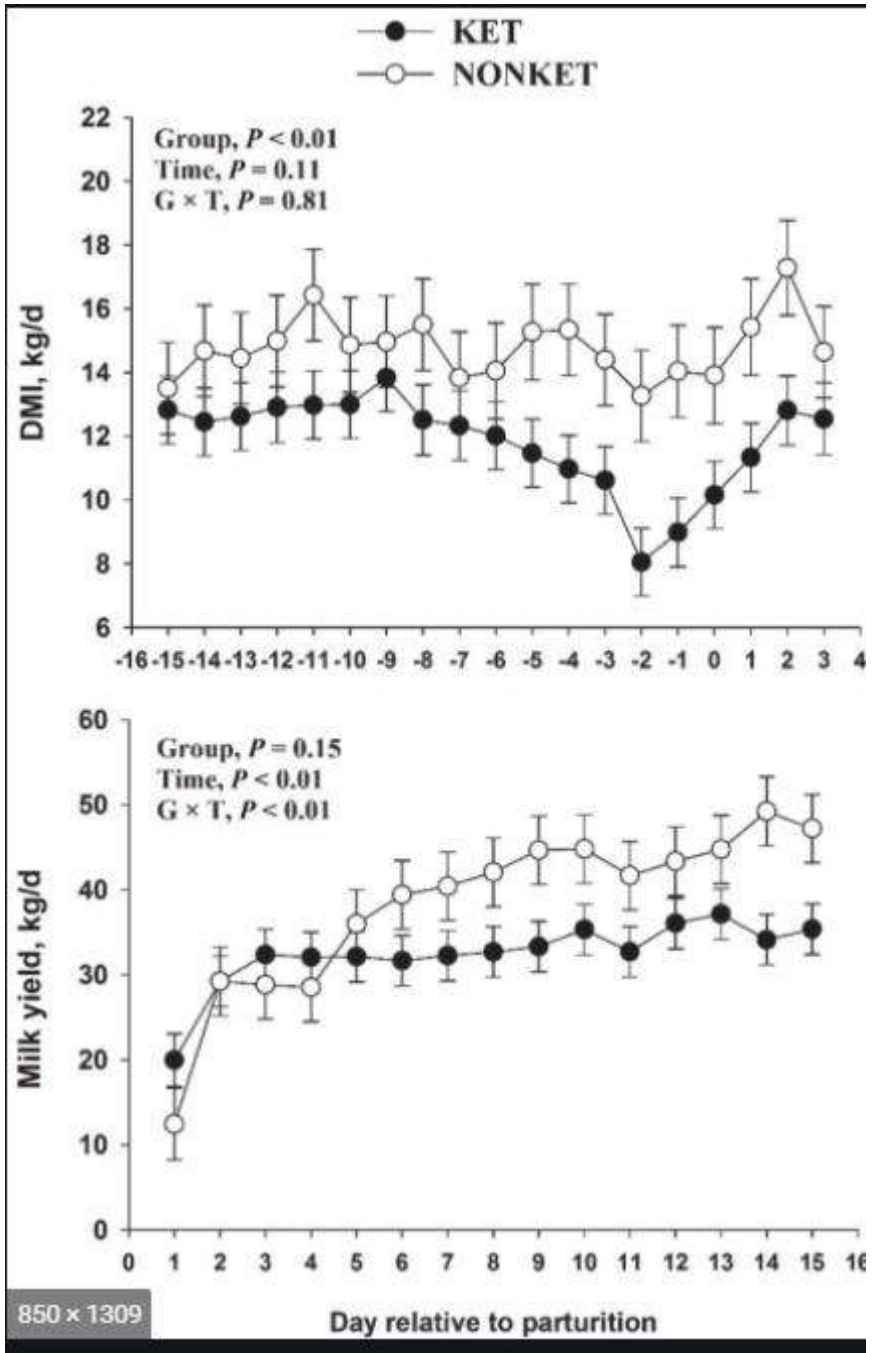
Clinical Presentation

- If rations are offered in components, cows with ketosis often refuse grain before forage.
- In group-fed herds, reduced milk production, lethargy, and an “empty” appearing abdomen are usually the signs of ketosis noticed first.
- Sudden rise in milk fat is also one of the warning signs
- CNS disturbances are noted in a minority of cases. These include abnormal licking and chewing, with cows sometimes chewing incessantly on pipes and other objects in their surroundings.
- Incoordination and gait abnormalities occasionally are seen, as are aggression and bellowing.

Weight loss in ketosis

Diagnostic Tests

- Test kits are based on the presence of acetoacetate or acetone in milk or urine.
- Rothers' Test / Modified Rothera's test
- Dipstick tests available for human should not be used
- In urine ketone are present in most lactating cows, even in ketosis the concentrations are always higher than milk ketone body concentrations.
- Trace to mildly positive results for the presence of ketone bodies in urine do not signify clinical ketosis.
- Unless there are signs the urine test should not be regarded as positive.
- **Acetate / acetoacetate**
- **In buffaloes BHB concentration is more than acetate and acetoacetate**



Treatment Strategies

- Treatment of ketosis is aimed at re-establishing normoglycemia and reducing serum ketone body concentrations.
- **Bolus IV administration of 500 mL of 50%** dextrose, hyperosmotic avoid perivascular, vitamin B Complex (180 g = 2.8 MJ) = 20 L – 220 MJ
- Bolus glucose therapy generally results in rapid recovery, especially in cases occurring near peak lactation (type I ketosis). However, the effect frequently is transient, and relapses are common.
- Administration of glucocorticoids, including dexamethasone or isoflupredone acetate at 5–20 mg/dose, IM, may result in a more sustained response, relative to glucose alone.
- Supplementation of starchy feed- Ground maize, Jowar, Rice

Treatment continued

- Glucose and glucocorticoid therapy may be repeated daily as necessary.
- **Propylene glycol administered orally (250–400 g/dose)** once per day acts as a glucose precursor and is effective as ketosis therapy. Indeed, propylene glycol appears to be the most well documented of the various therapies for ketosis. Should not be overdosed
- **Type II ketosis** - More refractory to therapy
- In these cases, a long-acting insulin preparation given IM at 150–200 IU/day may be beneficial. Insulin suppresses both adipose mobilization and ketogenesis but should be given in combination with glucose or a glucocorticoid to prevent hypoglycemia.
- Use of insulin in this manner is an extra-label, unapproved use.
- Reduce milking- every 12 h 50-75% milk to be drawn

Prevention

- **Prevention** should start from late lactation cows – more energy supply from digestible fibre , Reducing body condition in the dry period, particularly in the late dry period, may even be counterproductive - excessive adipose mobilization prepartum.
- NFE in the feed should not exceed 25% in the first month
- A critical area in ketosis prevention is **maintaining and promoting feed** intake. Cows tend to reduce feed consumption in the last 3 week of gestation. Minimize this reduction.
- Monensin 300 mg in feed, Ammonium lactate- 60-120 g daily for a month with calcium propionate, Protected choline
- Bypass choline- Carnitine- Important for utilization of fatty acids into energy

What determines Feed intake in cows?

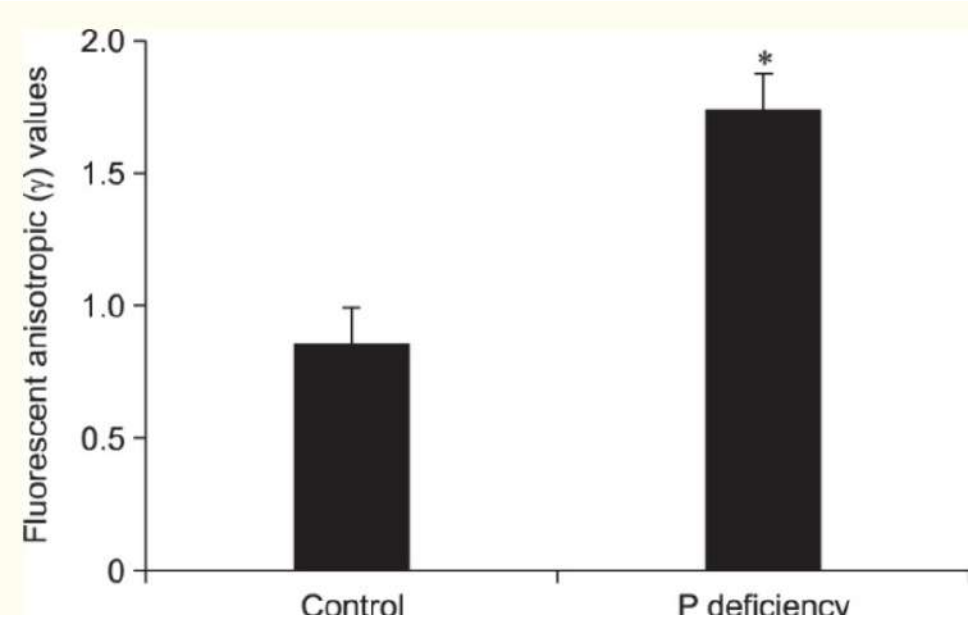
- NDF level in the feed determines the DM intake
- Post-calving the NDF should not exceed 25% of the total fibre content
- Typical feeding standard-
  - 500 kg weight Dry mater intake 2.5% target to increase it to 3.2% of the body weight by peak - protein 18-20% and NDF <33% of the total fibre
  - Maintenance energy – 54 MJ
  - For milk 3.8% fat - 5.7 per L milk produced, if more fat then could go up to 7 MJ / L milk

Hypophosphatemia- Chronic P Deficiency Syndrome

- When soil is deficient the P content fodder is low- High nitrogen fertilizers
- Feed deficient in grains- high alfalfa- feeding – P deficiency
- Osteoporosis – rickets – bone density
- Pica
- Sub-fertility- delayed maturity, anoestrus, abnormal calving, abortions
- Phosphorus is essential for metabolism- ATP-hence part of energy metabolism
- Haemolytic syndrome
- Daily requirement of P is around 15-16 g for maintenance and 1.25 g per kg milk but bioavailability is 45-50% hence around 40 g P supplementation is necessary
- DM intake dependent-before and after calving DM intake is reduced-

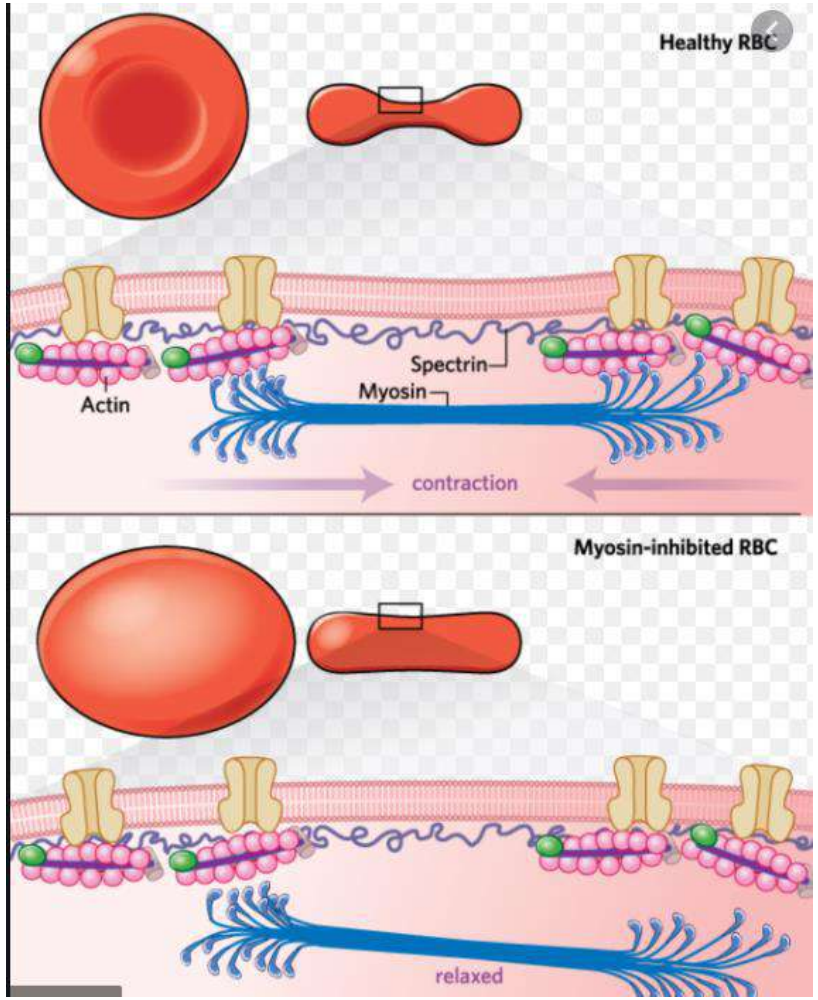
Pathogenesis

- Inorganic phosphorus is critical to uptake of glucose by red blood cells
- Glucose is the only energy source – converted to Phosphorus
- RBCs do not have mitochondria (nucleus) hence anaerobic pathway of production of ATP
- ATP needed for shape change of RBCS when passing through small capillaries, if rigid these starts breaking
- Release of Haemoglobin
- Heinz bodies leads to extravascular hemolysis



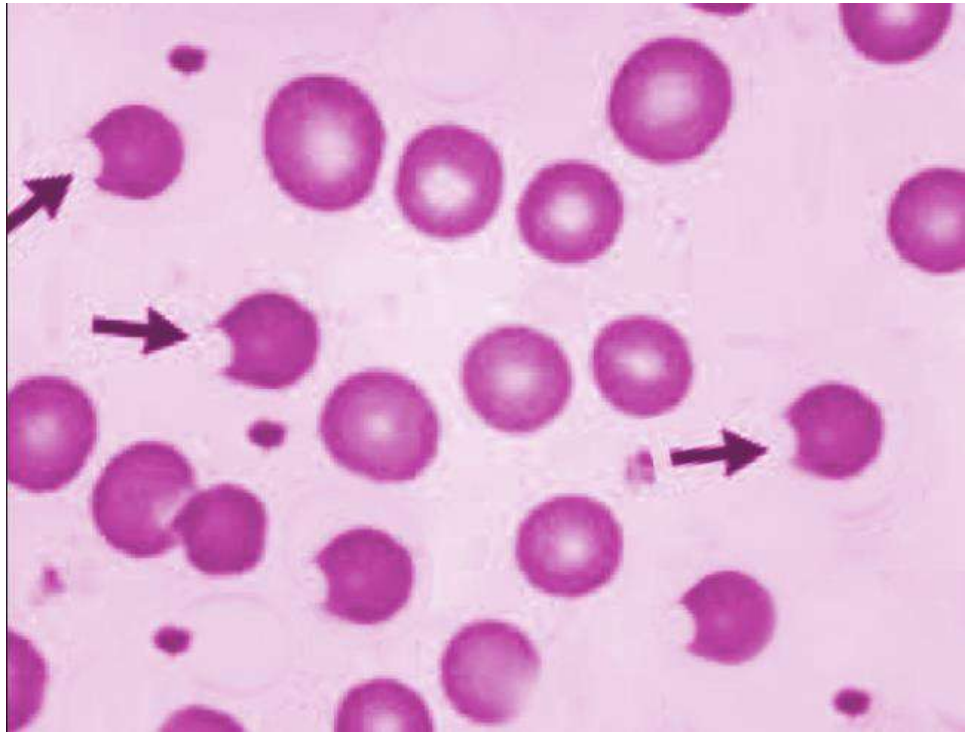
Pathogenesis

- When the red cells pass through small capillaries of size less than RBCs, the cells change their shape, using actomyosin in the cell wall
- The pressure signal induces ATP-induced shape transition
- If cells become rigid these start breaking



Diagnostic Tests

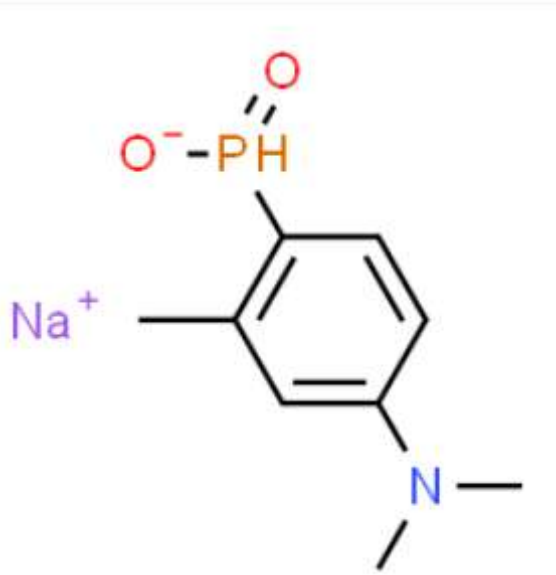
- Serum inorganic phosphorus- 6-8 mg / dl –but not a good indicator
- Total blood phosphorus – Better indicator as cellular phosphorus is affected first and then Pi
- In areas where soil P is low, P-deficiency haemoglobinuria is a common syndrome
- In many cases haemoglobinuria may not be recorded – but Heinz bodies in erythrocytes are common



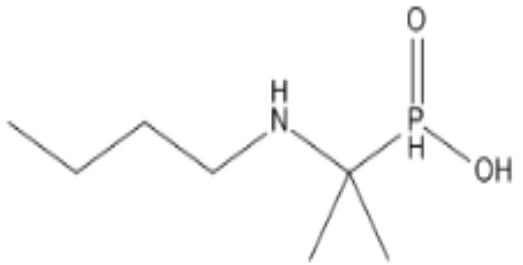
Treatment

- In haemolytic syndrome replenishment of P is important:
  - Stimulate uptake of glucose
  - Stimulate ATP synthesis
  - Resolve Heinz bodies
- Organic Phosphinates: (Tonophosphan)
  - No rationale for its use
  - Phosphinate compound, P=O bond, 15 ml = 220 mg P
- Monosodium acid phosphate – Not suitable compound- highly acidic pKa – 3.2, 5.4, 10.2
- Buffered Phosphorus, inosine, pyruvate- stimulates ATP synthesis
- Novizac – Intas
- Tonophosphan – No rationale for its use
  - Phosphinate compound, C-P bond, 15 ml = 220 mg P
- **Read my blog in indiancattle.com**

Toldimphos
Molecular Weight
180.1



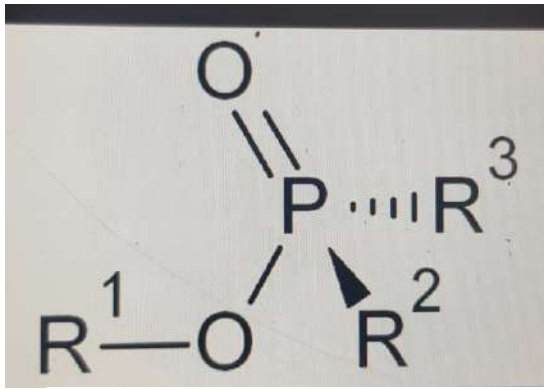
Butaphosphan
MW-1550.6

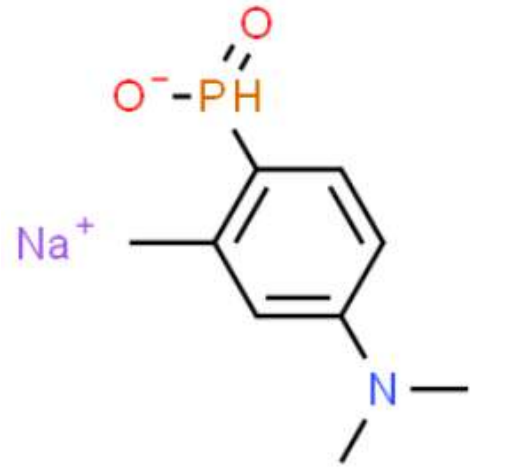


$C_{70}H_{106}CoN_{15}O_{17}P_2$

Tonophosphan- MSD –Vet Manual

'In cattle, solutions containing not phosphate, but phosphinate (PO3), hyophosphite or organic phosphorous compounds such as butaphosphan or toldimphos are often used to supplement phosphorous i.v., frequently in combination with Ca, Mg and other minerals. However, these phosphorous compounds are not suitable to correct hypophosphatemia, because mammals are unable to convert phosphite or other above-mentioned organic compounds into phosphate (PO4) and so do not contribute to the biologically active plasma pool. Even when organic phosphate compounds are usable metabolized, pharmaceutical product containing organic phosphate compound administered at the label dose does not provide enough phosphorous to cover serum phosphorus depletion, which would be a primary indication for i.v. treatment'.





Prevention

- Oral supplementation of Phosphorus- Feed P-rich proteins, such as cottonseed cake, soybean cake, maize gluten, etc.
- If the diet is rich in alfa alfa, special care is required
- Rice straw is rich in phosphorous but bioavailability is low
- Spraying of superphosphate one kg dissolved in 5 L water, stirred well and allowed to settle for 12 hours, supernatant can be used as source of phosphorus
- Monitoring of total cellular phosphorus in blood every six months in randomly selected cows is a better monitoring test

Milk Fever

- Milk fever is typically associated with calving. It is not due to deficiency of calcium but a temporary problem where calcium from the body is not mobilized to make for losses in colostrum synthesis.
- As a rule. Majority of clinical cases (75%) therefore would be recorded within 3 days of calving (sometime even 24 to 48 hours before calving) and around 10-15% cases between 4 to 7 days after calving and 5% between day 8^{th} to day 15 after calving.
- Very rarely classical milk fever cases would be seen after 15 days of parturition. Time of calving is most important evidence for diagnosis. In India milk fever is more frequent in buffaloes compared to cows.
- In some cows haemoglactia is one of the signs of hypocalcaemia- Check blood clotting time, add Ca to stimulate

Diagnosis

- Three phases: Tetany, Sternal Recumbency, Lateral Recumbency
- In cows where colostrum synthesis has started before calving and udder is full with milk. Such cows may show symptoms of hypocalcaemia and one of the prominent sign is uterine inertia (that is no uterine contraction).
- Blood Coagulation Defects

Treatment

- **Treatment:** The most critical part in treatment is ‘SPEED’. Milk Fever should be regarded as emergency and treatment must be started at the earliest- muscle and nerve damage- ‘Downer’s’.
- Ideally after diagnosis treatment should start within one hour.
- In case the veterinarian is not available to administer intravenous the farmer should attempt intramuscular injection of dicationic calcium (such as Sancalvet).
- Oral dosing may not help as rumen motility is low
- The drug of choice for uncomplicated cases is calcium boro-gluconate to be given intravenous. Usually response is dramatic, even with half of the dose the animal would get up and start feeding.
- **Too much calcium can** also weaken the heart muscles. 85% of **cows** respond to **one** treatment; **many** rise within 10 minutes and others 2-4 hours later. **Giving one** bottle IV and another under the skin **does** not affect recurrence rate (25%) and **can** increase the likelihood of 'downer **cow** syndrome’.
- Slow injection is important to avoid heart complications. Rapid administration of calcium will cause cardiac fibrillation for which antidote is magnesium sulphate intravenous.

Treatment

- How many times calcium should be injected and what should be the dose are highly debated questions? From my own experience first choice of drug is calcium borogluconate 300-450 ml administered intravenously, slowly over a period of 30-45 minutes.
- When only calcium is administered it is know to cause anorexia- DM intake will go down- hence should be careful- With Mg- this side effect is not there.
- In case the animal has responded to intravenous with partial injection (say half of the dose)
- Stop intravenous injection and the balance injection I give sub-cutaneous. When calcium is given intravenous most of it is excreted in urine. S/c injection

Indication of Ca- Mg- Borogluconate

Composition:

Calcium	1.86% w/v.
(as Calcium Gluconate I.P.)	
Magnesium Hypophosphite	5.0% w/v
Anhydrous Dextrose I.P.	20.0% w/v
Chlorocresol I.P.	0.1% w/v
(as preservative)	

Miphocal is recommended in the treatment of milk fever due to hypo calcaemia or when it is associated with hypo magnesaemia and hypo phosphataemia.

Indication

Mifex is primarily a drug of choice for the treatment of Milk Fever or associated deficiencies of Magnesium & Phosphrous

Mifex offers Calcium,Magnesium & Phosphrous in most ideal proportions to meet the normal requirement of the lactating cow. Dextrose in Mifex helps maintain protein and carbohydrate metabolism during lactation and combats Acetonemia.

Composition

Contains :

CAlcium borogluconate toghether with Magnesium & Phosphrous in organic combination and Dextrose.

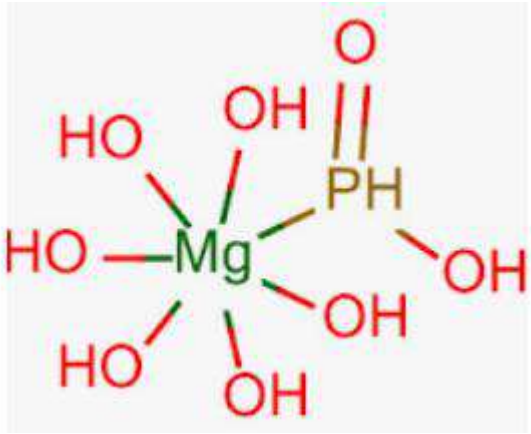
Dosage

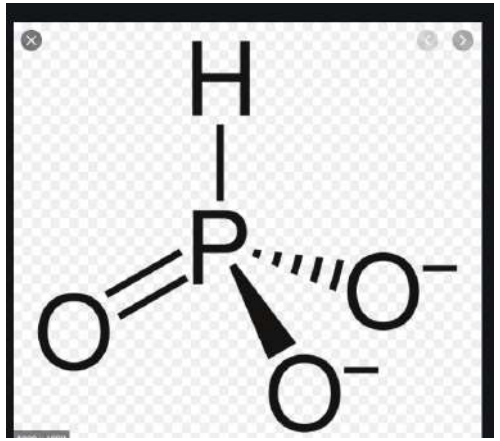
Canine:

N/A

Magnesium Hyophosphite is not a source of phosphorous

- How to diagnose Mg deficiency?
- When animal is in third stage that is in lying position (unresponsive to external stimuli) and muscle twitching is still persistent
- Products like Mifex although claim in their literature it does not replenish P as Mg-hypophosphite can not be hydrolysed to release P
- When to prefer combination depends on the stage of the disease.
- In Down cow I prefer calcium borogluconate followed after 2 hours by sodium phosphate in 5% glucose
- I have been able to get good response with Vitamin D3 injection in refractive cases of milk fever. Hypocalcaemic cows into calving will start uterine contraction immediately after calcium administration
- Calcium injections are also most abused injection in animals used irrationally. Calcium injections are not galactagogue hence should not be used to increase milk yield or easy let down of milk. It works only when there is specific indication.
- In Downers Cow, you get better results if calcium is followed by buffered phosphorous - Novizac





Prevention

- Recurrence in 5% cases- if more than 2% cases, review the feeding and mineral feeding strategy.
- The current recommendation is that during the dry period cows / buffaloes should be given different types of mineral mixture, that is less of cation and more of anions, whereas after calving this needs to be reversed.
- There is a product available in the market (Biochlor) which has been found to reduce incidence of milk fever and other transition associated metabolic disorders. But remember one thumb rule, do not feed lactation mineral mixture during dry period and vice versa.

- **THANK YOU**

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