Medial patella luxation (MPL) is a common developmental orthopaedic condition of the canine patient. Small breed dogs are more commonly affected by the condition than large breed dogs. Patella luxation also occurs in large breeds dogs with medial luxation occurring more commonly than lateral luxation. Medial patella luxation can also be seen in cats the surgical management is similar to that of dogs.

**DIAGNOSIS**

Medial patella luxation is easily detected clinically by palpat ing the patella with the leg in extension and feeling the patella luxating medially to the trochlear groove. These patients are usually young, under a year of age.

Radiographs are generally used to rule out any other conditions which may be present. It is essential to radiograph these patients for 2 reasons. Firstly, in middle age patients it is less likely for the patella to be clinically significant and the clinician should make sure there is no other condition such as cranial cruciate ligament disease. The other reason for radiographs is that the patella luxation may be the result of more complicated conformational conditions. These patients will usually have associated musculoskeletal abnormalities, including medial displacement of the quadriceps muscle group, distal femoral varus (Fig 1), hypoplasia of the medial condyle and rotation tibial deformity.

Clinically these patients have been graded as to the degree of patella luxation through the full range of motion (Table 1). This grading system takes into account the effects of the other components of the condition by their effect on the patella. The grading system does not however quantify the underlying components of the condition which may have lead to the patella luxation. The big concern is that a grade 2 or 3 luxation can be present in a patient with a marked femoral varus and in another patient with only a mild femoral varus. This grading does not thus allow us to accurately determine the best way forward in regards to surgical treatment of each individual patient. Grade 4 patients mostly have moderate to severe bony deformities that need correcting.

**PATHOGENESIS**

There are many suggestions put forward to explain how MPL occurs. Some authors suggest that the pathogenesis differs in small breed and large breed dogs. A reasonable suggestion is that MPL develops from a decreased angle of inclination of the femoral neck, coxa vara. This leads to marked angular deformities of the distal femur from bowing of the distal femur, genu varum. This causes a relative tibial varus and internal rotation of the tibia on the femur. The patella is then forced medially due to the pull of the medial thigh muscles and hypoplasia of the medial condyle.
Table 1. Grading Patella luxation in the dog

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Patella can be luxated but spontaneous luxation seldom occurs. Once the patella has been luxated during clinical exam, the patella spontaneously reduces when the examiner releases pressure. The patella is stable in the trochlear in full range of motion</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Angular and rotation deformities of the femur may be present. The patella can be luxated and remains luxated through full range of motion unless reduced by the examiner. The animal can clinically reduce the patella and this is seen with the skipping gait. Once reduced the patella remains in the trochlear groove for the full range of stifl e motion</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Angular and rotational deformities are often present. The patella remains luxated most of the time. The patella can be reduced by the examiner however normal range of motion of the stifl e lead to luxation of the patella</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Moderate to severe angular limb deformities are often present. The patella is permanently luxated and cannot be reduced to the trochlear groove at any point in the normal range of motion of the stifl e. The trochlear groove itself is often shallow or convex</td>
</tr>
</tbody>
</table>

condyle. Other studies have shown an increased angle of inclination of the femoral neck is associated with patella luxation in small breed dogs. Large breed dogs seem to have a relatively normal conformation of the femur when compared with small breed dogs. However large breed dogs with MPL tend to have a relative degree of patella alta (high-riding patella - structurally found more proximal in the trochlear groove) when compared to the conformation of normal large breed dogs, this may be cause or consequence of MPL in large breed dogs.

SURGICAL REPAIR

Surgical repair of patella luxation should be performed on animals showing clinical signs of lameness associated with the patella luxation or in young animals to prevent the long-term complications later on in life from the patella luxation. The main goal of surgical repair is re-alignment of the patella-quadriceps mechanism leading to normal sliding of the patella in the patella groove. Surgical repair has two categories, a release or an augmentation of the soft tissue components and corrective distal femoral osteotomy (CDFO) or tibial crest transplant (TCT).

It has been shown that soft tissue procedures performed without correction of the bone deformities have a high failure rate and should never be used as a sole method of repair. Surgical complications using the current techniques are reported as high as 85-48%. Surgical complications using the TCT in combination with soft tissue repair techniques are reported to be as high as 20%. These complication rates should be considered to high for a condition that is relatively common. (Fig 2a, 2b)
Surgical repair most often utilizes a combination of soft tissue and bone repair to reposition the patella in the trochlear groove. The trochlear groove can then be deepened using one of the many described techniques for a trochlearplasty. Only techniques that salvage the cartilage in the trochlear groove should be used.

Newer methods of creating a deeper trochlear groove have been developed in recent times. These consist of RidgeStop™ developed by Orthomed UK (Fig 3). This uses a high-density polyurethane implant placed on the medial trochlear ridge to aid in the treatment of patella luxation. The current recommendation is that it should only be used alone in cases of mild patella luxations with no marked bone deformity of the leg. It can be used together with the bone corrective techniques to augment repair.

The RidgeStop™ offers a less invasive method to deepen the patella groove to aid in movement of the patella in the normal alignment. It does not require the removal of a cartilage wedge to deepen the groove but does require accurate placement of 3 bone screws in the medial condyle to secure the implant. Kyron have developed an entire groove replacement made from titanium that the patella slides in. The author has no experience with this technique.

The disadvantage to both these techniques is the increased cost to the client for the surgery. The implant is significantly more expensive than a trochlearplasty. This should be discussed with the client on a case to case basis. Our recent experience with Ridgestop™ is that it provides an adequate method for deepening the trochlear groove with less damage to the cartilage.

Given the high complication rates of soft tissue procedures performed on their own, it is recommended that they should always be combined with re-alignment of the bony structures. A tibial crest transplant has been the standard operation used for re-alignment of the bony structures.

This technique is simple to perform but can have catastrophic complications. The complication rate varies from 9-50% for a tibial crest transplant. The most common complication is recurrence of the patella luxation which requires surgery in around 20% of cases.

A corrective distal femoral osteotomy was until recent times only used for severe cases of patella luxation with a severe femoral varus and severe patella luxation. In these cases a guarded prognosis was given even though the animals did improve clinically but were never normal. However recently CDFO has gained popularity in correction of patella luxations with a moderate femoral varus (Fig 4a,b).

The challenge comes in patient selection for a TCT or CDFO. Most patients presenting with a patella luxation will have plain film radiographs as an initial step after the clinical exam. Plain film radiographs were shown to be 96% accurate in ruling a patient out of having a CDFO but only 76% accurate in patient selection for a CDFO. This was performed measuring the R-aLDFA of the femur, which was found to be an acceptable measurement to assess the varus deformity. R-aLDFA is a measurement made on radiographs to determine the center of rotation.
of the distal femur, CORA in order to perform a corrective osteotomy. It stands for the anatomic lateral distal femoral angle. The technique for measurement can be found in most surgical texts.

However in the 20% of cases we see major complications it can be a nightmare to repair. Major complications require a corrective surgery with additional cost to the owner and morbidity to the animal. These complications can be symptomatic return of the patella luxation, tibial crest fracture, infection or tibia fracture. Implant migration is often seen and even though it requires another surgical procedure to remove it will often not affect the outcome once clinical union has occurred.

The 60% of dogs that develop a recurrent patella luxation at 4-6 weeks post TCT often are asymptomatic. Most of these will not require corrective surgery unless symptomatic as previously stated.

The underlying question is what harm is this recurrent patella luxation doing to the articular cartilage down the line?

The big challenge and hope of this lecture is that the surgeon will no longer apply 1 surgical technique to all patients with patella luxations. Instead then we should be assessing the underlying anatomical deformities of the patient and plan the surgery from there. The author suspects the high failure rate for TCT, up to 50%, is caused by this technique being used in all patients presenting with medial patella luxation without thought to the underlying anatomical deformities leading to or exacerbating the patella luxation.

Hopefully with further studies on the initial cause of patella luxation in young dogs and the long term outcomes of CDFO we can develop a treatment modality that gives us an excellent outcome in surgically correcting patella luxations.

It is recommended, given the extra cost to the client, that patients which are radiographically selected for a CDFO should have a computed tomography scan performed of the femur and the R-aLDFA should be measured on the CT images. This gives the most accurate measurement of the femoral deformity in all planes. This allows the surgeon accurate planning for the surgery and gives the best possible outcome.

The reality of patella luxation surgery is that we don’t understand the cause of the disease in these patients hence the conflicting literature on how to fix it. Current evidence, be it only a few small studies, is pointing towards a lower complication rate with CDFO than TCT. This needs to be further evaluated to help us provide the best options for our patients. The reality is that the TCT with associated soft tissue procedures is an excellent surgical procedure in 80% of cases.
Are all Generics Created Equal?

Bioequivalence is the comparison of the plasma profile between the test and reference product. A generic product is bioequivalent to the innovator product and it thus essentially identical, in a species group. There is no pharmacokinetic evidence to support human medicines being generics for veterinary species.

Introduction

A good way to start this article, would be for you to close your eyes and contemplate the valuable role veterinarians play in the health and welfare of animals. At this point, you would probably agree that veterinarians play an invaluable role of the diagnosis and treatment of animal disease or disease conditions. However have you ever considered what the function of the veterinarian would be, if we as a profession, had no medication available to treat our patients? Probably very little, and even less so since the profession has moved away from the use of Materia Medica (books describing how to prepare one's own medicines). So what has changed? The answer is simple and reflects our acceptance of modern pharmaceutical science as the means of treating disease.

These prepared formulations offer a number of benefits over practice-based drug preparations. These include:
• Ready availability (e.g. does not need to be prepared which save times and the need to keep raw ingredients as in an apothecary);
• they have long shelf lives (which means one does not need to keep restocking with new/fresh ingredients);
• one could rely on the use of synthetic chemicals (that would otherwise not be readily available)
• purer formulations (in that they’re not contaminated with foreign material or bacteria);
• potential for parenteral administration for rapid or sustained effect (since they’re sterile and pure) and lastly,
• they control for variable effects that can result from inconsistencies in absorption. All of which is possible through our better understanding of various aspects in pharmacology, such the drug’s pharmacokinetic profile, mechanisms of action, the interaction between pharmacokinetics and effect and the importance of biopharmaceuticals in the effects of medication.

Pharmacokinetics

Pharmacokinetics is the study of the movement of drug through the body, from the site of administration, to the site of effect and finally to the method of elimination. Of these absorption is dependent on the site of administration, the amount administered, the ability to body to remove the drug before it is absorbed and drug’s chemical profile. Similar factors determine whether the drug gets to the site of action, while elimination is dependent on the need for the drug to be metabolised or excreted.

The processes involved in the pharmacokinetics of a drug are studied by following the change in concentration of drug in the plasma over time (Figure 1). Using differential calculus, one can follow the change characteristics of the curve and establish mathematically how the drug is absorbed, distributed and/or eliminated. In pharmacokinetics the key controlling aspect is the drug formulation which controls absorption and elimination, and the endogenous/systemic processes which control elimination.

Figure 1 is a typical plasma concentration versus time that results following extravascular administration of a drug. A: is the absorptive phase; B: a combination of the absorptive and distributive phase and C: The elimination phase. The dotted line represents the relationship of the plasma concentration with the effect concentration (For the latter, one can see that it’s not...
only the ability to reach said concentration that is important, but the duration of time that the concentration can be achieved).

As one can see, since the drug concentration at the receptor site is important, and that the drug pharmacokinetics determines the drug concentration in the body, these two processes must interact to produce a drug effect. More importantly this principle states that if two drugs achieve the same concentration in the plasma, they should be equally as effective.

The formulation

Medication that are sold commercially, are sold as a mixture of ingredients that all interact to allow the said drug to have its effect. The formulation is there to ensure that the drug is adequately absorbed into the circulation and it can also control the rate of absorption. To place this into perspective, the formulation controls the time to a drug’s first effect, the degree of effect and thus the degree of side effects. The formulation has a number of potential components, which all fulfill different roles in allowing the active ingredient to be absorbed, as well as the shelf-life of the drug (Table 1).

Another important feature of the formulation is the actual chemical properties of the active ingredient, which also has an impact on drug absorption, chemical stability, interaction with excipients and at times even activity. For the latter it’s important to note that the active ingredient can also occur in different forms (e.g. amorphous versus crystalline) with some chemical forms being ineffective. The same can apply for chirals (L and D Isomers) with some isomers being inactive, more active or even toxic (e.g. dexmedetomidine is the active chiral of medetomidine).

In the formulation, the actives and inactives will interact with one another to control absorption (Figure 2).

From numerous pharmaceutical studies, we know that a change in the excipients or a change in the ratio of ingredients can result in different absorption profiles between formulations. The same can be said if a different form of the active (e.g. different salt, different size of molecular, different polymorph, different isomer) is in use.

As a given rule, no two formulations are identical until proven i.e. simply being told that formulation has the same active as another product is not sufficient to assume efficacy. This would need to be proven with validate methodology such as bioequivalence testing. Another important factor to be consider is the potential for the inactive and active to interact with one another with resultant inactivation, or change in tabletting pressure that precludes the release of the active ingredient in the same period of time, or even the incorrect pH which can cause pain and tissue damage on administration.

Since we know that the formulation effect is extremely important, drug manufacturers have to ensure that their formulations are as uniform as possible. Most try and keep their drugs within a 5% variation of the expected from batch to batch (e.g a 5mg tablet may have 4.75 to 5.25 mg therein), which is lower than natural variation which can be as high as 10%. This process of control is known as Good Manufacturing Practice (GMP), and involves standardising as many factors as possible, from how the chemicals are sourced to how the equipment is handled, serviced and calibrated. It expects the manufacturer to undertake routine assays of their formulation at various steps in manufacture as well to ensure that staff are adequately trained.

Other important aspects include the source and purity of the chemicals in use e.g. what’s the purity, is it free of endotoxins, is it free of contaminants, is it free of bacteria, etc. While this process does add to the costs of production, it is well known that without these control measures the variation in the formulation can result in unpredictable variations in plasma concentrations, which could translate to ineffective treatment, treatment being toxic or even inconsistent treatment where one dose works and another fails.
In the regulatory system, medicines general fall into three categories: Innovator products, Generic products and Compounded products. These three categories are controlled by the Medicines and Related Substance Control Act (Act 101 of 1965):

- **Innovator Products**: Are the first products that are brought onto the market. They are tested as the final formulation to prove that the active ingredient is properly released and that the formulation is effective. When registered, each indication is looked at individually and requires testing usually with actual clinical cases. The innovator company is generally allowed a period of 20 years from patenting, to sell their product with no competition. It is during this period that they recoup their investment. At all times, the manufacturer has to meet strict GMP requirements.

- **A Generic formulation**: Is a formulation that contains the same active ingredient as the innovator, and is registered through an abbreviated process known as bioequivalence or occasionally therapeutic equivalence. For the former process, the pharmacokinetics of the generic formulation is compared to the innovator formulation. If the two formulations can be statistically proven to be bioequivalent, it can be registered as a generic to the innovator product. The underlying principle comes from the pharmacokinetic-pharmacodynamic interactions of the active mentioned above. If the two drugs allow for the same plasma concentration to be consistently achieved, there’s no reason that they won’t have the same effect. Since we do know that the manufacture of the formulation can influence the plasma pharmacokinetics, the formulation has to meet strict GMP conditions, to ensure batch to batch uniformity. Generics are thus cheaper than the innovator because they don’t have to redo the efficacy and toxicity tests, as these have already been undertaken by the innovator company i.e. why retest for aspects that are already known. Since the pharmacokinetics of the generic formulation is unknown, this is what needs to be tested (Figure 3). With this said, the requirements for comparing the pharmacokinetic profiles of the generic to the innovator formulation is still very strict and has to comply with numerous requirements from the study design to the analytical chemistry part of the study.

The principle of generic registration is considered to
be highly sound, and has been used to bring numerous generic medications onto the market over the last 40 years, with no proof existing that a generic is inferior when used for its registered indication. The science is so sound, that the innovator company also relies on the same methodology when they want to change their formulation e.g. when a tablet is changed to a palatable tablet, bioequivalence testing is used to save on costs and prevent retesting as once again, there is no need to repeat all the tests. All in all, if a generic formulation is registered and the company follows GMP, there should be no difference between a generic and an innovator.

Nonetheless an important concept in generic medication development is the concept of switchability and prescribability.

- **Generics are interchangeable and any of the registered formulation for a particular species can be considered a valid effective choice at the start or initiation of treatment in a patient. This is known as prescribability i.e. the choice is open when the drug is first prescribed.**

- **However this scenario changes when one is treating a chronic condition where the patient has been stabilised on treatment with a particular formulation e.g. epilepsy. Under these conditions, it is not advisable to switch formulations acutely (irrespective of whether it a generic or innovator) acutely. This acute switching can only occur if the products are tested for switchability, which most formulations are not e.g. one can chose to use formulation A or formulation B initially (at this stage there is no difference). However at the end of the month, stick to the same formulation and don’t change acutely as this can be dangerous and result in destabilisation (i.e. for chronic patients, stock the same formulation). If you do need to change formulation, it’s always safer to phase out the old formulation while the new formulation is phased in.**

- **Compounded formulations: These are formulations that are meant for use in an individual patient and are tailor made drugs, usually made by a pharmacist on an “as needed” basis. Compounded formulations are generally simple formulations with the active dispersed in an excipient. These compounded products, due to their individualised nature, don’t need to legally comply with GMP requirements, and thus may be open to all the problems mentioned above. For this reason, the use of compounded products from a safety point to the patient and consumer, should not be used when there are alternate registered products i.e. legally one takes responsibility for the use. More importantly, it may be more difficult legally to demonstrate that the use of the compounded product use was prudent when there are GMP approved alternates available. Also of importance to consider is the product’s stability and purity and shelf life. Since this may be a problem, compounded products should ideally be limited to oral or topical use, and they should not be used in production animals.**

Is a Generic, definitely a generic?

This may seem as an odd question, in light of what has been said above. But it’s important to know the constraints of the process of bioequivalence. The foremost principle of bioequivalence is the comparison of the plasma profile between the test and reference product, and show that they’re essentially identical. However as mentioned under pharmacokinetics, the PK of a drug is dependent on a number of factors such as absorption and elimination. This would mean that the profile is dependent on the species of testing and the metabolism of the drug. As such, when bioequivalence is shown, each profile has to be determined for each the different route recommended and in each of the different species it is indicated for. As an example, a drug recommended for use by the subcutaneous and intramuscular in pigs, cattle and horses, will need to be tested in six separate studies to show that all the routes per species are bioequivalent. Since it may not always be possible demonstrate bioequivalence in all these studies, some generic formulations will have curtailed claims. As such it is important to check what the recommendation are on the package instead of assuming that they are the same as the innovator (reference product).

Another important consideration is the use of human medication in animals. Firstly this extra-label use of the drugs has legal implications, as the person recommending this use, takes responsibility if something goes wrong (for registered veterinary drugs used correctly as stated on the package insert, the registration owner takes responsibility). The use of human drug extra-label is nonetheless considered safer than using a compounded product, as good manufacturing practice is still in place as it’s a registered human product (i.e. same liability, but lower risk) (Table 2).

As a veterinarian, it is incumbent on you to make use of your professional judgement when choosing to use a human formulation. Firstly consideration must be given to the dose, which means that one needs to take into consideration the studies that have demonstrated that this extra-label use is prudent. For the latter consideration needs to be given to the sample size, as registered product use a substantial number of clinical cases to prove that the effect is real (as large as a few hundred animals) i.e. the published study on extra-label use may only have included a small number of clinical cases and not taken into consideration intra-subject variability in effect and side effects. Another important consideration would be that the product used in the publication, may not necessarily be the same product that is sold locally e.g. There are numerous cases of companies choosing to market different formulations in different countries for various manufacturing reasons even though the name is the same. It is possible that the published formulation may have a different response to the South African available drug, purely because they are of different formulation.
Another important scenario that comes up in South Africa is the cost of the medication. Under some conditions, veterinary medications may be more expensive than their medical generics, due to lower costs on the medical side from larger scale production. Can one use these human generics as cheaper therapeutic options? Firstly legally, the onus is on the treating veterinarian to let the owner know that there is a veterinary formulation and give them the option. The reason for this, is that the medical product has been tested in only people and thus the veterinary profile may be unknown i.e. it may be possible that the drug has different profiles in the veterinary patient than in people.

When the GI of man is compared to animals, there are major differences that can influence absorption between the species. These differences may be anatomical in that there are different structure of the GI; there may be differences in transit times; differences in content and thus non-specific binding; differences in bile salts; differences in pH amongst the different areas; differences in GIT bacterial content and/or species; differences in liver metabolic capacity; and most importantly differences in the transport proteins in the intestinal wall. The latter is also a major reason why veterinary drugs differ so much between species.

To illustrate the process, the innovator veterinary formulation of amoxycillin-clavulanate and Ran-Clav® (Ranbaxy) were compared at the same dose and the same route in the same six Beagles (in a cross-over study undertaken by myself). (Figure 4) The result for amoxycillin phase of the study showed a marked difference in absorptive profile between the two formulations. While the small sample size did result in significant variability in both groups, this was much more substantial (>80%) in the Ran-Clav® group. This study illustrates the point that the non-veterinary formulation could not only differ in the extent of absorption, but more importantly could result in large intra-subject variability which could mean completely inferior treatment in some individuals. This effect is addition to being potential dangerous, is also generally unknown until tested.

**Conclusion**

Drug regulation science, is a highly complex science that is focused on allowing the treating veterinarian the best chance of getting therapeutic success in a patient with the least chance of formulation failure. This science extends to both innovator and generic formulations, but only so far as to the species and indication for which the product has been tested. As such, when using a non-veterinary formulation, care should be practiced, as therapeutic success are affected by a number of unknown variables such as added excipients and exact structure of the active chemical/ingredient.

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<tr>
<th>Category</th>
<th>Use</th>
<th>Benefits</th>
<th>Dangers</th>
<th>Liabilities</th>
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<tbody>
<tr>
<td>Innovator Vet Medicine/Stock Remedy</td>
<td>Registered Use</td>
<td>Proven safety, quality and efficacy</td>
<td>Poor storage can change product safety</td>
<td>If used and stored as per instructions. Falls to the manufacturer</td>
</tr>
<tr>
<td>Generic Vet Medicines/Stock Remedies</td>
<td>Registered Use</td>
<td>Proven safety, quality and efficacy</td>
<td>Poor storage can change product safety</td>
<td>If used and stored as per instructions. Falls to the manufacturer</td>
</tr>
<tr>
<td>Stock Remedies: Vet Med (innovator or generic) used extralabel</td>
<td>Used for non-registered purpose in the intended species</td>
<td>Proven quality. Safety known in target species if used at the recommended dose</td>
<td>Unknown efficacy when used for a new indication and potentially safety concerns when used at a different dose</td>
<td>Vet liable for extralabel use, since use is in the intended species i.e. species safety usually known</td>
</tr>
<tr>
<td>Stock Remedies: Vet Med (innovator or generic) used extralabel</td>
<td>Used for non-registered purposes in a non-indicated species</td>
<td>Quality of the product proven</td>
<td>Unknown efficacy as used for a new indication, and unknown safety concerns as used in untested species</td>
<td>Vet liable for extralabel use. Risk increases as species safety usually unknown</td>
</tr>
<tr>
<td>Human Meds</td>
<td>Non-registered use</td>
<td>Quality of the product proven</td>
<td>Unknown efficacy and safety</td>
<td>Vet liable for extralabel use. Risks are the same as use of a veterinary medicine in non-indicated species</td>
</tr>
<tr>
<td>Compound Meds</td>
<td>Non-registered product</td>
<td>Patient specific treatment option when no registered product is available</td>
<td>Unknown safety, efficacy and quality</td>
<td>Vet liable for use. Greater risk than extralabel use, since quality, safety and efficacy unknown</td>
</tr>
</tbody>
</table>

**Table 2:** Indication of how personal liability increases as different categories of medicines are used.

Figure 4: Average plasma concentration versus time profile for amoxycillin for a veterinary (R) and non-veterinary (T) amoxycillin formulation tested in the same group of six dogs in a 2x2 cross over study.