Cardiac glycoside intoxication

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TABLE OF CONTENTS

Introduction ................................................................................................................... 3

Poisonous principles................................................................................................................. 3

Epidemiology ......................................................................................................................... 3

Bufadienolide-containing plants .................................................................................. 4

*Moraea pallida* (yellow “tulp”/ “geel tulp”) ................................................................. 4

*Moraea miniata* (red “tulp”/ “rooi tulp”) ........................................................................ 5

*Moraea polystachya* (blue “tulp”/ “blou tulp”) ............................................................... 6

*Drimia sanguinea* (“Transvaal slangkop”) ..................................................................... 7

*Thesium lineatum* (“vaalstorm”, “witsorm”) and *Thesium namaquense* (poison bush, “gifbossie”) ............................................................................................................................ 8

Cardenolide-containing plants ..................................................................................... 9

*Nerium oleander* (oleander/”selonsroos”) .................................................................... 9

*Gomphocarpus fruticosus* (milkweed/“melkbos”) ............................................................ 9

Absorption and disposition ........................................................................................ 11

Mechanism of action ............................................................................................................. 11

Acute cardiac glycoside intoxication ........................................................................ 12

Clinical signs ....................................................................................................................... 12

Gastro-intestinal tract ....................................................................................................... 12

Cardiovascular system .................................................................................................... 12

Neuromuscular system .................................................................................................... 12
Cardiac glycoside intoxication

Respiratory system ...................................................................................................................... 13
Macroscopic and histopathology ............................................................................................. 13
Diagnosis .................................................................................................................................... 13
Treatment .................................................................................................................................... 14
Prevention .................................................................................................................................... 14
Conditioned feed aversion ........................................................................................................... 14
Vaccination .................................................................................................................................. 14
Differential diagnoses ............................................................................................................. 15

Cumulative bufadienolide poisoning ....................................................................................... 15
“Krimpsiekte” (Cotyledonosis) ................................................................................................. 15
Cotyledon orbiculata (pigs ears/“hondeoor-plakkie”) ............................................................... 16
Tylecodon wallichii (nenta/“kandelaarsbos”) ......................................................................... 17
Kalanchoe lanceolata (“plakkie”) ............................................................................................. 18
Epidemiology ............................................................................................................................. 19
Clinical signs ............................................................................................................................. 19
Treatment and prevention ......................................................................................................... 20

References .................................................................................................................................. 21
INTRODUCTION

Poisoning of livestock by cardiac glycoside-containing plants has the greatest economic impact of all plant-associated poisonings in South Africa. Collectively they are held responsible for 33% of all mortalities from plant poisonings of cattle and 10% of those in small stock.

Poisonous principles

Cardiac glycosides are organic molecules consisting of a genin or aglycone with one or more sugars attached. Chemically, two major groups of cardiac glycosides, namely the cardenolides and bufadienolides, are recognized. The cardenolides contain a single unsaturated, 5-membered lactone ring attached to C-17 and the bufadienolides a double unsaturated, 6-membered lactone ring attached to C-17 (Fig. 1). It is interesting to note that certain toads that occur in South Africa (11 *Bufo* species) secrete bufadienolides, catecholamines and tryptamine alkaloids in body fluids to protect themselves against predators.

![Epoxyscilliroside and Oleandrin](image)

**Fig 1:** The chemical structure of the aglycones of epoxyscilliroside, a non-cumulative bufadienolide, contained by *Moraea pallida* (yellow “tulp”) and oleandrin, a cardenolide type of cardiac glycoside, isolated from *Nerium oleander* (oleander).

Epidemiology

Poisoning of livestock by bufadienolide-containing plants, which surpasses cardenolide-induced poisonings in importance, may either be acute or chronic. “Tulp” poisoning (induced by various *Moraea* species) and “slangkop” poisoning (caused by various *Drimia* species) induce only acute intoxication as these species contain non-cumulative bufadienolides. “Tulp” poisoning is the most important plant-associated poisoning in cattle in South Africa and occurs throughout the country. Poisoning occurs predominantly in newly introduced or hungry stock and in young, naive animals. An
important feature of yellow “tulp” (*Moraea pallida*) poisoning is that stock that grows up on “tulp”-infested veld can learn to avoid the plant. “Tulp” is an important hay contaminant as it remains toxic upon desiccation. Livestock are frequently poisoned following ingestion of hay or milled hay contaminated by “tulp”. Intoxication has also been reported where horses were exposed to *Eragrostis* hay and lucerne contaminated with “tulp”.

On the other hand, members of three genera of the Crassulaceae (*Cotyledon*, *Tylecodon* and *Kalanchoe*), generally referred to as “plakkies”, contain cumulative, neurotoxic bufadienolides and may cause either acute or chronic poisoning. The chronic form of the poisoning is colloquially referred to as “krimpsiekte” and is primarily a disease of small stock.

**BUFADIENOLIDE-CONTAINING PLANTS**

Plants often incriminated in poisoning are members of four families namely Iridaceae (e.g. “tulp”); Hyacinthaceae (e.g. “slangkop”); Santalaceae (e.g. “witstorm”) and Crassulaceae (e.g. “plakkies”).

*Moraea pallida* (yellow “tulp”/ “geel tulp”)

The aerial parts sprout annually from a perennial corm during autumn. The mature plant has a single, long leathery leaf that bends towards the ground. The leaf blade has prominent parallel venation (Fig. 2a). The blade is usually flat, but is sometimes folded while the base encloses the flowering stalk in a sheath. A single, branched inflorescence is produced and the yellow flowers, consisting of six petals are star-shaped (Fig. 2b). The flowering period is from September to October.

![Fig 2a: Flowering yellow “tulp” (*Moraea pallida*). The leaf blade has prominent parallel venation.](image)

![Fig 2b: Yellow, star-shaped flowers of *Moraea pallida* (yellow “tulp”).](image)
M. pallida is widely distributed in South Africa (Fig. 3) and grows in a variety of soil types and under various climatic conditions. The plant is exceptionally invasive and colonizes disturbed soil such as maize lands and trampled areas.

*Moraea miniata* (red “tulp”)

Red “tulp” also sprouts annually from the perennial corm. It differs from yellow “tulp” as more than one leaf is usually formed (1-4 leaves per plant) and the leaf blades are slightly wider. The flowers are similar to those of yellow “tulp” and the petals are usually pink in colour with a distinct yellow, star-shaped marking in the centre of the flower (Fig. 4). The flowering time lasts from the end of August until the end of October. This species occurs mainly in the southern and south-western parts of the country in a wide range of soil types, and in very dry areas as well as in those with a high rainfall (Fig. 3).
Moraea polystachya (blue “tulp”/ “blou tulp”)

This plant has a perennial corm and annual aerial parts usually consisting of four elongated leaves which form a sheath around the base of the inflorescence. The flowers are iris-like with three larger flat petals and three smaller upright petals. The flowers are blue-mauve in colour with a yellow spot at the base of each of the three larger outer petals (Fig. 5). Moraea polystachya is widespread in the middle of the country (Fig. 6).

The blue “tulp” is distinctly different from most other “tulp” species as it flowers in autumn and winter, usually from April to June. The species is very invasive, particularly in over-grazed, trampled areas, and once it is established it is very difficult to eradicate.

It should be noted that there are various other Moraea species, but they are of lesser veterinary importance. However, these species should be regarded as potentially toxic.
**Drimia sanguinea** ("Transvaal slangkop")

The "Transvaal slangkop" is a perennial bulbous plant with annual aerial parts. The bulb is reddish brown in colour (Fig 7a) and is just below the surface of the soil. The inflorescence arises first, before the rains, and bears numerous small white flowers with a greenish or brownish stripe down the middle of each petal (Fig. 7b). The leaves, which appear after the inflorescence, are grey-green in colour. The species is widely distributed in southern Africa and grows in a variety of soil types (Fig. 8).

**Fig. 7a:** The reddish brown bulb of *Drimia sanguinea* ("Transvaal slangkop").

**Fig. 7b:** Numerous small white flowers of *Drimia sanguinea* ("Transvaal slangkop"), notice the greenish stripe down the middle of each flower petal.

**Fig. 8:** Distribution of *Drimia sanguinea* ("Transvaal slangkop").
(Courtesy of SANBI).
Cardiac glycoside intoxication

Other *Drimia* species such as *D. altissima* ("maerman") and *D. physodes* are occasionally implicated in intoxication.

*Thesium lineatum* ("vaalstorm", "witsorm") and *Thesium namaquense* (poison bush, "gifbossie")

These two species are small, woody, perennial shrubs, up to 1 m high, with many thin, straight, greenish branches. The small alternate leaves are much reduced. The small flowers are yellowish white and after fertilization small spherical fruits form (Fig. 9). These species are often implicated in small stock losses in the Great Karoo.

![Fig. 9: Thin, straight, greenish branches of a *Thesium* species containing small spherical fruits.](image-url)
CARDENOLIDE-CONTAINING PLANTS

*Nerium oleander* (oleander/“selonsroos”)

The oleander is a much-branched shrub often planted in gardens or along highways. The leaves are narrow and leathery. The flowers are produced at the tips of the branches and there are various colour varieties (Fig. 10).

![Fig. 10: The pink colour variety of Nerium oleander (oleander/“selonsroos”).](image)

The oleander is indigenous to eastern Europe and Asia and have been known for centuries to be toxic to man and beast. All parts of the plant and even the smoke when it is burned are poisonous. The dried plant in hay or fodder can also cause poisoning. Animals may even die if they should drink water in which leaves or flowers of the plant have fallen. A few leaves are sufficient to cause the death of a sheep. Fortunately oleander is rarely browsed by animals and only cause incidental poisoning of cattle and sheep. Horses were affected when they were tied next to a fence and browsed on the leaves. Dogs are susceptible and young puppies may ingest this plant in the garden when they are teething.

*Gomphocarpus fruticosus* (milkweed/“melkbos”)

Milkweed is an indigenous plant that has become a troublesome weed. It occurs throughout the country on roadsides and in disturbed areas. Milkweed is a much branched shrub and secretes white latex when damaged. The leaves are opposite, narrow, with pointed tips. The white flowers are borne in clusters and hang down. The fruit is inflated, balloon-like, and covered with long hair-like processes (Fig. 11).
There are various other plant species that contain cardenolides such as *Thevetia peruviana* (yellow oleander/"geeloleander"), *Acokanthera* spp. (Bushman’s poison bush, “boesmangif”) and *Digitalis* spp. (foxglove/"vingerhoedkruid"), but they are not of major importance with respect to poisoning of livestock.

There are even insects such as the Monarch butterfly/"melkbos skoenlapper" (*Danaus chryssipus*) and the “stinksprinkaan” (*Phymateus leprosus*) who feed on milkweeds or oleander and accumulate cardiac glycosides in their bodies as a defense against predators.
Cardiac glycoside intoxication

**ABSORPTION AND DISPOSITION**

Absorption, metabolism and excretion depend on the individual characteristics of the specific compounds involved and vary greatly. Cardiac glycosides are broken down (detoxified) by rumen micro-organisms, but when poisoning results the animal has invariably ingested an overdose. All the cardiac glycosides are sufficiently lipid soluble to be absorbed in lethal quantities from the gastrointestinal tract. These compounds are rapidly absorbed and stock can die peracutely within hours, but it is mainly considered an acute poisoning. The cardiac glycosides are widely distributed and can cross the blood-brain barrier. Some compounds are readily metabolized and excreted; some are excreted unchanged whereas others are extremely cumulative (see “kripsieke”). The half-life depends on the specific cardiac glycoside involved and varies greatly, thus the half-life may either be relative short or prolonged.

**MECHANISM OF ACTION**

Cardiac glycosides inhibit the Na\(^+\)/K\(^-\)-ATPase enzyme on the surface of the outer cell membrane. When the Na\(^+\)-K\(^-\) pump is inhibited there is a lack of energy and a relative accumulation of Na\(^+\) inside and K\(^-\) outside the cell. Usually Ca\(^2+\) is pumped out and Na\(^+\) into the cell by the Na\(^+\)/Ca\(^2+\) exchanger, but due to the high intracellular Na\(^+\) concentration this exchange is halted and Ca\(^2+\) accumulates intracellularly (Fig 12). These ionic disturbances interfere with the transmembrane potential of the cells and consequently there are conduction disturbances e.g. arrhythmias. Hyperkalaemia also occurs.

![Diagram](image)

**Fig. 12:** The cardiac glycosides inhibit the Na\(^+\)/K\(^-\)-ATPase enzyme on the surface of the outer cell membrane which results in transmembrane ionic disturbances.
ACUTE CARDIAC GLYCOSIDE INTOXICATION

Clinical signs

Four organ systems are mainly affected.

Gastro-intestinal tract

In general ruminants poisoned with “tulp” presents with ruminal atony, stasis and bloat. With the exception of the red “tulp” (that causes constipation) there is often diarrhoea that may even be haemorrhagic during the later stages in the course of the disease. In livestock that has ingested “slangkop” the diarrhoea may only be transient or even absent.

Cardiovascular system

The cardiac glycosides have a negative chronotropic effect and initially a bradycardia (also attributed to the hyperkalaemia) and bradyarrhythmias may be discernable, however, the heart rate soon accelerates and tachyarrhythmias are audible on auscultation. On electrocardiography (ECG) ventricular ectopy, ventricular tachycardia, flutter and fibrillation are recorded.

The negative dromotropic effect attributed to these compounds induces 1st, 2nd and 3rd degree atrio-ventricular blocks and atrio-ventricular dissociation. These are explained as both a direct effect due to changes in the transmembrane potential and an indirect (vagotonic) effect.

Neuromuscular system

When the animals are mustered the affected animals are lagging behind the rest of the herd or flock. More severely affected animals may even be disinclined to move. Cattle that are still ambulatory exhibit typical posterior paresis (weakness of the hind quarters) (Fig. 13), which invariably progress to paralysis and the animal lies in ventral recumbency. Whole body tremors are also present.

Occasionally some animals may be restless, appear nervous, hypersensitive and incoordinated. Torticollis is often reported in stock that have been poisoned with “plakkies” (“krimpsiekte” – see below) and “slangkop”.

Cardiac glycoside intoxication
Respiratory system

Initially an expiratory grunt can be audible and later dyspnoea or even periods of apnoea will indicate severe pulmonary dysfunction.

Macroscopic and histopathology

At necropsy no specific gross lesions are noticed and the post mortem may be regarded as rather negative. Non-specific changes such as generalized congestion, subepi- and endocardial and subcutaneous haemorrhages, lung oedema and emphysema, ruminal atony and hyperaemia of the intestinal mucosa are reported. If the animal has died peracutely leaf remnants may still be present in the rumen. “Tulp” leaves (tough, fibrous and strongly ribbed leaf) as well as oleander (hard leathery leaves) may be discerned in the rumen contents.

On microscopical examination myocardial degeneration or even necrosis and pulmonary oedema are present. In more chronic cases foci of myocardial fibrosis are seen.

Diagnosis

There are various criteria that are important to reach a diagnosis. A history of young naive animals or livestock newly introduced to the area should raise suspicion. The clinical signs, necropsy findings and histopathology report could all aid in a diagnosis. Check for the presence of the plants in the camps and whether it has been eaten.
Cardiac glycoside intoxication

Treatment

Activated charcoal at a dose of 2 g/kg live weight is very effective. A large dose is essential to effectively adsorb and bind the excess plant toxins in the rumen. Furthermore, retro-diffusion (movement of absorbed toxins back from the circulation into the gastro-intestinal tract) has been described. An “universal antidote” should not be used as it might contain too much tannic acid which will de-activate the charcoal.

Nevertheless, farmers should be warned that the excessive stress of restraining and dosing the clinically affected animal might induce fatal cardiac disturbances. After dosing minimize stress to prevent catecholamine release and keep the animals calm and rested in a kraal or small paddock.

Additional treatment for valuable animals could include anti-arrhythmic drugs such as lignocaine and β-blockers and atropine to antagonize the vagal effects, however, more research studies are required. Certain therapeutic approaches are in fact contra-indicated. Do not administer calcium solutions, adrenalin or potassium (unless hypokalaemic).

Prevention

Poisoning is usually controlled by fencing off infested areas. Eradication of plants by using herbicides e.g. glyphosate (“Round-up”) for “tulp” or the manual removal by digging up “slangkop” can be attempted.

Conditioned feed aversion

Stock that grows up on “tulp”-infested veld can learn to avoid the plant and develops a form of cognitive aversion. When sub-lethal amounts of yellow “tulp” are ingested aversion is induced. This aversion is strong, therefore poisoning usually occurs only in animals newly introduced from non-infested areas or young, naive stock. Research demonstrated that cattle could be artificially averted to yellow “tulp”. The application of this technique was confirmed in cattle grazing yellow “tulp”-infested pastures and M. pallida-infested harvested maize lands.

Aversion was induced by dosing an aversive mixture consisting of epoxyscillirosidin (the toxin and natural aversive substance of M. pallida), a lithium salt (which served as the complementary aversive substance) and a “tulp” hexane extract (which served as identification factor for the “tulp”).

Vaccination

A practical way to control “tulp” poisoning could be by immunization of animals. A “tulp” vaccine will most probably protect livestock from “tulp” poisoning. If a prophylactic vaccine
Cardiac glycoside intoxication

(consisting of the plant toxin [epoxyscilliroside] conjugated to a protein plus an adjuvant) can be produced the incidence of and mortalities caused by “Tulp” poisoning in livestock could be curtailed.

Differential diagnoses

There are various other intoxications that induce peracute to acute mortalities that should be ruled out. Other cardiac poisonings such as ionophore antibiotics, “gousiekte”, “gifblaar”, as well as urea, prussic acid and nitrate/nitrite poisonings are examples. Infectious causes such as black quarter, anthrax and heartwater should also be considered.

CUMULATIVE BUFADIENOLIDE POISONING

“Krimpsiekte” (Cotyledonosis)

The majority of the cardiac glycoside poisonings in small stock is ascribed to “krimpsiekte”, which is one of the limiting factors for small stock production in the Little Karoo and southern fringes of the Great Karoo in South Africa (Fig. 14).

Members of three genera of the Crassulaceae (Cotyledon, Tylecodon and Kalanchoe), generally referred to as “plakkies”, may cause either acute or chronic poisoning. “Krimpsiekte”, the chronic form of the poisoning, occurs predominantly in small stock. This toxicosis is caused by cumulative bufadienolides, which have neurotoxic properties unique to these compounds in the Crassulaceae. In
this syndrome the cardiac, respiratory and gastro-intestinal signs, typical of acute cardiac glycoside poisoning, diminish and the neuromuscular signs dominate. “Krimpsiekte” is a paretic, neuromuscular condition.

*Cotyledon orbiculata* (pigs ears/“hondeoor-plakkie”)

This succulent plant has thick stems. The permanent fleshy leaves are round and grey-green in colour with a red margin (Fig. 15a). There are various varieties such as *C. orbiculata* var. *dactylopsis* and *C. orbiculata* var. *oblonga*. The bell-shaped flowers are five-merous (five fused flower petals), orange-red in colour and pendulous (Fig. 15b). This “plakkie” has an extensive distribution area in the country and grows in a wide variety of soil-types often on hills or mountain slopes (Fig 16).
Fig 16: Distribution of *Cotyledon orbiculata and *Cotyledon barbeyi in South Africa. (Courtesy of SANBI).

*Tylecodon wallichii* (nental/"kandelaarsbos")

This much branched, deciduous, succulent bush has thick stems covered with woody remnants where the leaves have fallen off (old leaf scars) (Fig. 17a). The finger-like grey-green leaves are at the ends of branches (Fig 17b). The inflorescences bear small, greenish-yellow, bell-shaped flowers that are pendulous. Flowers are also five-merous. The flowering time is from November to February and the plants are usually in large communities. The "kandelaarsbos" occurs in the Western Cape Province and western semi-arid regions of the Northern Cape Province of South Africa (Fig. 18).
Kalanchoe lanceolata ("plakkie")

This erect, annual (or weakly perennial), succulent is up to 1 m high and often grows in dense communities in the shade of trees and bushes (Fig. 19a). The fleshy leaves are arranged oppositely. The flowers are four-merous, star-shaped and orange in colour (Fig. 19b). This plant occurs in the northern provinces of South Africa (Fig. 20).
Cardiac glycoside intoxication

Other *Tylecodon* species, such as *T. ventricosus* ("klipnenta") and *T. grandiflorus* ("rooisuikerboom") and other *Kalanchoe* species e.g. *K. rotundifolia* ("nentabos"), and *K. paniculata* ("krimpsiekte bossie") have also been implicated in poisoning.

**Epidemiology**

The incidence of "krimpsiekte" is highest in goats, but sheep are equally susceptible. Angoras reportedly are more prone to "krimpsiekte" than boer goats. Cattle and horses, though seldom exposed, can also contract the disease. Fowls are rarely affected but are quite susceptible. As is the case with other cardiac glycoside poisonings, newly introduced stock or naive animals are more likely to eat "plakkies" than local animals which tend to avoid the plant. Small stock of all ages and gender are susceptible, especially young and sub-adults probably because they graze with less discernment than older animals.

In some regions "krimpsiekte" occurs mainly during the winter and spring (May to September), while in others the incidence is highest in spring or early summer (July to late November), and during spells of summer drought. This variation is ascribed to seasonal differences, climatic conditions and plant species involved. "Krimpsiekte" can nevertheless, to a greater and lesser extent, occur throughout the year.

**Clinical signs**

Acute poisoning is also referred to as "opblaas krimpsiekte" and is similar to acute cardiac glycoside intoxication where the animals exhibit bloat and die suddenly.
Cardiac glycoside intoxication

Chronic poisoning is the typical “kripsiekte” syndrome. Chronic toxicity or “dun kripsiekte” in small stock follows a protracted acute attack or after repeated intake of small amounts of the plant. The animals are usually in poor condition, tire easily, lag behind the flock, walk with the head nodding or dangling loosely and they frequently lie down. Often they assume a characteristic stance, with the feet together, back arched and the head down, sometimes trembling (Fig. 21). Affected animals may lie, fully conscious, in a shaded spot for hours.

![Fig. 21: A sheep exhibiting the typical “kripsiekte” posture - feet close together, back arched and the head down.](image)

The muscles of the neck are affected, often giving rise to torticollis - one of the notable diagnostic features of “kripsiekte”. Frequent mouthing movements, drooping of the lower jaw, protrusions of the tongue, salivation and failure to masticate and swallow (resulting in half-chewed balls of ingesta in the mouth) have been recorded. In animals that can swallow, appetite remains good.

It should be noted that secondary (relay) poisoning has been induced in dogs by feeding them goat and horse livers and horsemeat obtained from “kripsiekte” carcasses.

**Treatment and prevention**

As no specific therapy is available, treatment is aimed at alleviating signs and supporting the animal. By judicious feeding, providing shade and not disturbing or exciting the animals, some recoveries can be expected. The only feasible method of preventing poisoning would be to eradicate the plant, but this is impractical owing to the low value of land in affected areas and the severe ecological impact of such measures. Where possible, camp off badly infested areas. Special care should be taken in the management of young and newly introduced stock. During droughts supplementary feeding will ensure that the animals consume less “plakkies”.

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Page 20
REFERENCES


