Krimpsiekte in South Africa: historical perspectives

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Abstract

Krimpsiekte, also known as *cotyledonosis* or *nenta*, in sheep and goats has been recognised as a disease entity since 1775. However, it was only in 1891 that Veterinary Surgeon Soga reproduced the condition by dosing *Cotyledon* (=*Tylecodon*) *ventricosus* leaves to goats. Professor MacOwan, a botanist, confirmed the identity of these nenta plants. From a South African veterinary toxicological point of view the date 1891 is of considerable historical significance since this was the first time that a plant was experimentally demonstrated to be toxic to livestock in South Africa. A chronological account of the history of krimpsiekte research is provided.

Introduction

Krimpsiekte, a paretic/paralytic condition in small stock, was one of the first diseases documented in South Africa and ascribed to a plant poisoning. Members of three genera of the succulent Crassulaceae family (*Cotyledon, Tylecodon* and *Kalanchoe*) and generally referred to as plakkies, have been incriminated as a cause of this poisoning. Krimpsiekte is a chronic form of cardiac glycoside poisoning, and various cumulative bufadienolides, with neurotoxic properties unique to these compounds, have been isolated over the years (Kellerman *et al.*, 2005). Krimpsiekte is the Afrikaans vernacular, can be directly translated as meaning "shrinking disease" and refers to the neuromuscular signs. Krimpsiekte is, arguably, the most important plant poisoning of small stock in the Little Karoo and southern fringes of the Great Karoo (Kellerman *et al.*, 1996). This paper provides a short synopsis of historical developments.

The early days

Historically, krimpsiekte has also been referred to as *nenta, t'nenta, t'nanta, c'nenta, rita, cotyledonosis* and kraamsiekte (Henning 1926; Hutcheon 1899; Steyn 1934; Watt & Breyer-Brandwijk 1962). Vahrmeijer (1981) states that krimpsiekte or nenta has been a serious problem in southern Africa since 1775, but no authentic documentation confirming this could be traced. Steyn (1934) cites Browne (1864), who referred to a disease called t'nanta, as the first official record of krimpsiekte. In 1884, Hutcheon induced the disease in two goats by dosing them with strained rumen liquor obtained from a goat with krimpsiekte. In 1877, the botanist MacOwan (Figure 1), as cited by Hutcheon (1899), erroneously implicated *Lessertia annularis* Burch, a legume, as the cause of 'rita' (krimpsiekte) in goats. Hutcheon also produced krimpsiekte in a dog by feeding it on the livers of affected goats. Hutcheon (1899) describes the result of his feeding experiment as follows: "The dog which was fed upon the livers developed acute symptoms of the disease in two days". This is the first report of secondary (relay) intoxication induced by krimpsiekte.

FIGURE 1: Prof Peter MacOwan (1830-1909).

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The aetiology of krimpsiekte was resolved only in 1891 when Veterinary Surgeon Soga produced the condition by dosing *Tylecodon ventricosus* leaves to goats. He determined that as little as 2 oz. (56,7 g) of freshly cut and shredded *T. ventricosus* leaves given on 3 consecutive days caused typical signs of the disease in 4 days and death in 6 days of commencement of dosing. All of the eight goats developed typical signs of krimpsiekte and six died (Soga

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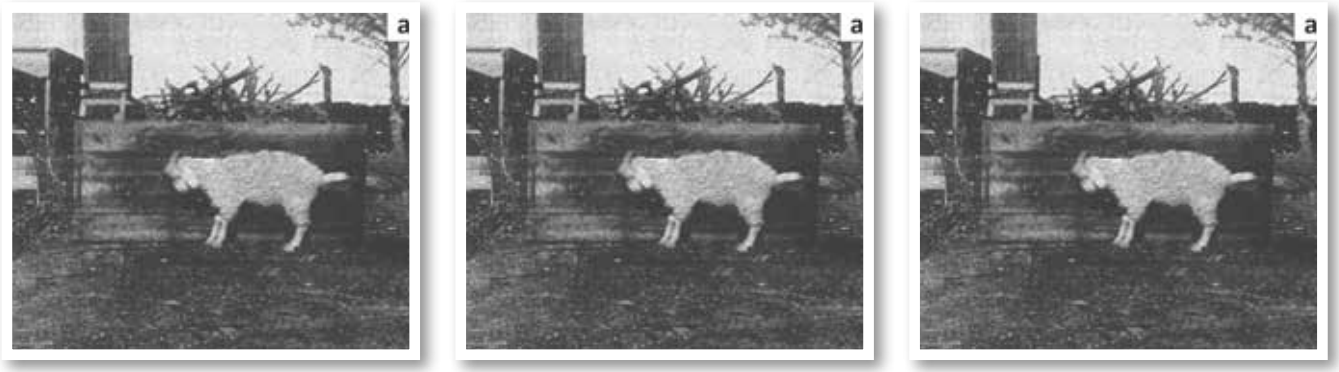

FIGURE 2: Photographs of goats suffering from krimpsiekte taken by Veterinary Surgeon Borthwick in 1898.

FIGURE 3: Dr Joseph Burtt Davy (1870-1940) seated in the centre and Miss Sydney Margaret Stent (1875-1942) seated to his right.

FIGURE 4: Dr HH Curson (circa 1933)

1891). Soga credited Mr Weyer of De Toekomst, Somerset East for incriminating this plant which he used in confirmatory dosing trials. Professor MacOwan identified these nenta plants as *Cotyledon ventricosa* Burm. Soga (1891), later renamed *Tylecodon ventricosus* (Burm. f.) Tölken (Tölken 1978). From a South African veterinary toxicological point of view the date 1891 is of considerable historical significance since this was the first time that a plant was experimentally demonstrated to be toxic to livestock in South Africa (Curson 1926).

Soga's results were nevertheless met with some scepticism because the trials were carried out with local goats in an endemic krimpsiekte area and no member of the Crassulaceae was previously known to be toxic. Later, veterinary surgeons Tomlinson, Borthwick and Dixon independently confirmed Soga's findings by feeding or drenching *T. ventricosus* to local goats in non-krimpsiekte areas (Hutcheon 1899). The historical photographs of goats suffering from 'nenta' or krimpsiekte (Figure 2) were taken by Borthwick in 1898 (Hutcheon 1899; Watt & Breyer-Brandwijk 1962).

The 1900s

The second member of the Crassulaceae family to be implicated in poisoning was *Cotyledon orbiculata*. In 1908 Dr Burtt Davy, the Government Agrostologist and Botanist and his herbarium assistant, Miss Stent, (Figure 3) related an incident of suspected poisoning of fowls with *C. orbiculata*. After thinning out *C. orbiculata* in her garden, a lady fed chopped leaves to her fowls. The following day six hens were dead and several others severely depressed. Burtt Davy also reported that Sir Arnold Theiler confirmed toxicity (paralysis and mortality) in two hens fed plant material obtained from the outbreak (Burtt Davy & Stent 1908). Kehoe (1912) administered 240 g *C. orbiculata* plant material to an Angora goat which developed clinical signs reminiscent of krimpsiekte and died 10 days later. He also induced *C. orbiculata* poisoning in fowls. In small stock, *C. orbiculata* can induce both acute and chronic (krimpsiekte) intoxication under natural conditions (Terblanche & Adelaar 1965; Tustin *et al*., 1984). Acute cardiac glycoside-poisoning in a flock of 16 Angora goat rams, of which six died, occurred after consumption of *C. orbiculata* (Tustin *et al*. 1984). *Cotyledon orbiculata* collected from a farm near Maltahöhe in Namibia, where sheep developed clinical signs resembling krimpsiekte, was dosed orally to sheep to confirm toxicity. A single dose of only 1.0 g/kg of this particular batch of plant material (semi-dried stems and leaves) was lethal for sheep. Strong indications of a cumulative effect were found, since as little as 50 mg/kg plant material daily (nine dosages over 13 days) produced intoxication (Terblanche & Adelaar 1965).

The second *Tylecodon* species to be implicated in the aetiology of krimpsiekte was *Tylecodon wallichii* (Harv.) Tölken subsp. wallichii (= *Cotyledon wallichii*. Harv.), proven toxic

by Curson (Figure 4) in 1920 (Curson 1926; Tölken 1978). Henning (1926) confirmed that this plant was highly toxic to goats, sheep, horses and even fowls. An adult goat, weighing 36 kg, was drenched with 7 g dried *T. wallichii* leaves on Day (D) 0 and again on D 6, representing a total dose of only 0.39 g/kg. Clinical signs developed 4 days later, mortality ensuing 2 days after the commencement of clinical signs. In another trial, an adult goat (38 kg) was poisoned by 17 g minced fresh leaves administered over 25 days. A 3-month-old goat kid also died within 7 days of receiving 24 g minced flowers. Henning concluded that when livestock were administered relatively large doses of plant material in a comparatively short period, acute intoxication resulted, sometimes referred to as 'opblaas' krimpsiekte in the field. On the other hand, when small doses were repeatedly given over an extended period, clinical signs more typical of krimpsiekte were produced. Henning (1926) also induced secondary poisoning in dogs by feeding them goat and horse livers and horsemeat obtained from krimpsiekte carcasses.

Acute cardiac glycoside poisoning in cattle in the Winter Rainfall Area has been ascribed to *T. grandiflorus* (Kellerman *et al.,* 2005). However, Anderson and co-workers reproduced krimpsiekte in sheep by repeated oral dosing of 0.5 - 1.0 g/kg fresh *T. grandiflorus* plant material (Anderson *et al*., 1983a).

The acute form of cardiac glycoside poisoning could also be induced by dosing dead/senescent or fresh dried *Kalanchoe lanceolata* plant material to sheep (Anderson *et al.,* 1983b) and feeding stems and leaves to a cow (Masvingwe & Mavenyengwa 1997). In the sheep, acute intoxication was induced by a single dose of 3.5 - 5 g/kg milled, dried plant material. However, ovine krimpsiekte, could not be induced by repeated administration of *K. lanceolata* plant material at lower doses. Mortality occurred in the cow after ingestion of approximately 15.5 g/kg fresh plant material (Anderson *et al*.,1983b; Masvingwe & Mavenyengwa 1997).

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Chemistry and toxicity

The first references to a possible toxic principle appeared in 1926 when Henning noted that the toxic principle in edible tissue was thermostable, not being destroyed at 120 °C for 15 minutes nor by boiling in water for 30 minutes. He further reported that the majority of the toxin was extracted with 60 % ethanol acidified with 1 % HCl (Henning 1926). In the same year Kamerman, primarily utilizing *C. orbiculata* plant material and comparing his results with other plakkies, isolated an amorphous, slightly bitter, colourless toxic compound found to be non-alkaloidal, non-glucosidal and nitrogen free. He assigned the provisional name, cotyledontoxin ($C_{32}H_{28}O_7$) to the compound and suggested that it belonged to the picrotoxin group of nerve poisons (Kamerman 1926). Gunn (1931) cited by Steyn (1934), reported that a 70 % alcohol extract of *T. ventricosus* produced a digitalis-like action on excised frog and rabbit organs. The intensity of action was about one-eighth that of digitalis (Steyn 1934).

Sapeika (1936) suggested that, besides the neurotoxic cotyledontoxin, toxic species also contained a substance, probably a glycoside, with the pharmacological properties of digitalis. The contradictory findings of Kamerman on the one hand and Gunn and Sapeika on the other were resolved some 40 years later when a bufadienolide cardiac glycoside, namely cotyledoside, was isolated from *T. wallichii* (Van Rooyen & Pieterse 1968; Van Wyk 1975). The oral and subcutaneous 48 h LD50 of cotyledoside for guinea-pigs was 0.173 mg/kg and 0.116 mg/kg, respectively (Naudé & Schultz 1982). These authors also induced acute and subacute poisoning and mortality in sheep following single intravenous injections of 0.05 - 0.1 mg/kg cotyledoside and chronic intoxication (krimpsiekte) after 2 - 5 consecutive daily intravenous administrations of 0.01 mg/kg cotyledoside (Naudé & Schultz 1982). In 1997 Botha and co-workers confirmed the presence of cotyledoside in *T. wallichii*. Two sheep were given cotyledoside (0.01 - 0.015 mg/kg body weight) intravenously on consecutive days, except during weekends. Both sheep developed typical krimpsiekte on Day 9 of the experiment which lasted until they were sacrificed (Botha *et al*., 1997).

In 1985, Anderson *et al.,* isolated four bufadienolides from *C. orbiculata*, namely tyledoside C and three new bufadienolides, orbicuside A, B and C (Anderson *et al.,* 1985; Steyn *et al*., 1986b). The approximate subcutaneous 24 h LD50s of orbicusides A, B, and C and tyledoside C for guinea-pigs were 0.1, 0.25, 0.25 and 0.2 mg/kg, respectively (Anderson *et al.,* 1985). Orbicuside A and tyledoside C had a mild cumulative effect in guinea-pigs after four daily subcutaneous injections of 50 per cent of the LD50. Five consecutive intravenous injections of 0.012 mg/kg orbicuside A to a sheep induced ruminal stasis, paresis and recumbency (Anderson *et al*., 1985).

The toxicological properties and toxins of *Tylecodon grandiflorus* (Burm. f.) Tölken have been thoroughly investigated by Anderson and co-workers. Six bufadienolides isolated from *T. grandiflorus* were characterized as tyledosides A, B, C, D, F and G (Anderson *et al*., 1983a; Steyn *et al.,* 1986a). Typical signs of krimpsiekte in a sheep were induced by repeated intravenous injection of 0.012 mg/kg tyledosides A and D. The approximate subcutaneous LD50 in guinea-pigs of tyledosides A and D was c 0.12 mg/kg, tyledoside C and E c 0.2 mg/kg and tyledoside F c 0.18 mg/kg. For three of these bufadienolides, namely tyledosides A, D and F, a cumulative effect in guinea-pigs could be demonstrated, but no such cumulative effects were evident with tyledosides C and E (Anderson *et al*., 1983a). In 1998, Botha *et al*. also isolated tyledoside D from *T. ventricosus* collected on a farm near Somerset-East in the

Eastern Cape Province.

The presence of cardiac glycosides in *K. lanceolata* was confirmed by the extraction and isolation of three bufadienolides: 3-O-acetylhellebrigenin (previously extracted from *Melianthus comosus*) was one of these and the other two (initially referred to as K 28 A and K 28 B) were designated lanceotoxin A and lanceotoxin B (Anderson *et al.,* 1983b; Anderson, *et al.,* 1984). Krimpsiekte could only be reproduced experimentally by repeated intravenous administration of 0.01 mg/kg lanceotoxin B and 0.02 mg/kg lanceotoxin A. The estimated subcutaneous LD50 of lanceotoxin A for guinea-pigs was c. 0.2 mg/kg, for lanceotoxin B c. 0.1 mg/kg and for 3-O-acetylhellebrigenin c. 0.36 mg/kg. A cumulative effect was demonstrated with lanceotoxin A and B, but 3-O-acetylhellebrigenin was non-cumulative (Anderson *et al*., 1983b; Anderson *et al*., 1984).

Acknowledgements

This paper was presented at the History Session of the 30th World Veterinary Congress at Cape Town in 2011 and subsequently published in the *Journal of the South African Veterinary Association* Vol 84, No 1 (2013), 5 pages. doi: 10.4102/jsava.v84i1.1059

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