CHAPTER 74

Toxicity of yew (Taxus spp.) alkaloids

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INTRODUCTION

Taxines, the principle toxic alkaloids derived from yew (Taxus spp.) plants, are responsible for numerous animal deaths each year. They are produced by members of the Taxus spp., evergreen trees or shrubs that are commonly used as ornamental landscaping plants. From their leaves and branches numerous taxine alkaloids have been isolated and characterized chemically. However, the degree of toxicity of each individual compound can vary. For the toxic members of the group, their primary mechanism of toxicity appears to be as antagonists of calcium channels in cardiac myocytes. This effect can cause disturbances in electrical conduction and rapid onset of adverse clinical signs often ending in death due to heart failure.

BACKGROUND

Plant characteristics

Yews (Taxus spp., Taxaceae) are evergreen plants often used for ornamental landscaping in many parts of the United States, Europe, and elsewhere throughout the world. Common varieties in the United States are English Yew (Taxus baccata), American Yew (Taxus canadensis), Japanese Yew (Taxus cuspidata), and Pacific or Western Yew (Taxus brevifolia), (Kingsbury, 1964). These plants can be highly toxic and have been implicated in human and animal poisonings. The poisonous taxine alkaloids have been reported to be present in the foliage, bark, and seeds of the plants, but not in the fleshy scarlet aril (berry) (Bryan-Brown, 1932; Kingsbury, 1964).

Historical references

References to yew toxicity date back over two millennia (Bryan-Brown, 1932). In the first century, B.C.E., Julius Caesar (102–44 B.C.E.) wrote of Catuvolcus, the king of Eburones, who poisoned himself with yew “juice” (Fröhne and Pfänder, 1984). Ancient Celts committed ritual suicides by drinking extracts from yew foliage and used the sap to poison the tips of their arrows during the Gaelic Wars (Foster and Duke, 1990; Hartzell, 1995). Some primitive cultures are reported to have used yew extracts as hunting and fishing aids (Watt and Breyer-Brandwijk, 1962; Hartzell, 1995). During the 18th and 19th centuries, decoctions of yew leaf were documented as having been used as an abortifacient or an emmenagogue by women in Europe and India (Bryan-Brown, 1932; Watt and Breyer-Brandwijk, 1962), however, toxic side effects stemming from these usages may also have occurred.

Chemical characterization

The first report of preparation of an amorphous, white, non-crystalline powder called, “taxine” was from analysis of yew foliage (Taxus baccata L.) for alkaloid content reported in 1856 by Lucas. It was isolated in crystalline form approximately 20 years later by Marmé, a French scientist (Hilger and Brande, 1890), but it wasn’t until 1956 that Graf and Boeddeker (1956) discovered that taxine was a mixture of heterogeneous compounds. Further investigations recognized two major types of taxine alkaloids: taxine A and taxine B (Graf, 1956).

By subjecting the taxine extracts to electrophoresis (Graf, 1956), two major bands were noted. The fastest
moving band was designated taxine A which comprised approximately 1.3% of the total alkaloid extract. The slower migrating band, taxine B, represented approximately 30% of the total alkaloid fraction extracted from *T. baccata* L. (Graf, 1956; Graf and Bertholdt, 1957). Subsequent analysis elucidated the molecular formula of taxine A as well as its basic physical and chemical properties (Graf and Bertholdt, 1957; Graf et al., 1982; and Table 74.1a and Figure 74.1a). The structural formula of taxine A was reported almost 25 years later (Graf, 1982) and an analog, 2-deacetyltaxine A (C₃₃H₄₅NO₉), from the leaves of *T. baccata* (Table 74.1b) in 1994 (Poupat et al., 1994; Figure 74.1b). The structure of taxine B was first reported in 1986 (Graf et al., 1986) which was slightly revised in 1991 (Ettouati et al., 1991; Table 74.1c and Figure 74.2a). Purified taxine fractions from *Taxus* spp. reveal the presence of several taxine B-related compounds. Isotaxine B (C₃₃H₄₅NO₈), a structural isomer of taxine B, is present as a major constituent in the alkaloid fractions (Poupat et al., 1994; Jenniskens et al., 1996; Adeline et al., 1997; Potier et al., 1997; Table 74.1d and Figure 74.2b). Present as minor constituents in *Taxus* spp. are 1-deoxytaxine B (Figure 74.2c) and 1-deoxyisotaxine B (Figure 74.2d) (Jenniskens et al., 1996; Potier et al., 1997). Also present as minor constituents, at approximately 2% of the total concentration, are the taxine B pseudoalkaloids 13-deoxy-13α-acetyloxy-taxine B (C₃₅H₄₉NO₁₀), 13-deoxy-13α-acetyloxy-1-deoxytaxine B (C₃₅H₄₉NO₁₀), and 13-deoxy-13α-acetyloxy-1-deoxy-nortaxine B (C₃₅H₄₉NO₁₀) (Appendino et al., 1997). Within the last decade the importance of the antineoplastic drug, taxol, a related member of the taxane diterpenoid family, has spurred the discovery and chemical characterization of over 350 members of this chemical class (Itokawa, 2003).

**PHARMACOKINETICS/TOXICOKINETICS**

For reasons probably related to their acute toxicity and the lack of pharmaceutical uses for the toxic taxine alkaloids, pharmacokinetic studies have not been published. However, extensive pharmacokinetic studies have been reported for the widely used antineoplastic drugs, paclitaxel (isolated from *T. brevifolia*) and docetaxel (synthesized via a taxane precursor from *Taxus baccata*), which are also members of the taxane diterpenoid family. In studies with these two compounds, it has been found that they are both highly protein bound (>95%) in the serum. In addition, paclitaxel exhibits non-linear kinetics at therapeutic doses while the kinetics of docetaxel are linear. They are both metabolized in the liver by cytochrome P450 enzymes. Work done with docetaxel indicates that this is primarily the result of metabolism by CYP3A4 to pharmacologically inactive oxidation products which are excreted in the bile through a *p*-glycoprotein-dependent

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**TABLE 74.1 Physical and chemical properties of taxine alkaloids**

<table>
<thead>
<tr>
<th>Taxines</th>
<th>Molecular formula</th>
<th>Melting point (°C)</th>
<th>Optical rotation</th>
<th>UV max (nm)</th>
<th>IR max (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Taxine A</td>
<td>C₃₅H₄₇NO₁₀</td>
<td>204–206</td>
<td>[α]D₂₀ = –140°</td>
<td>220, 255</td>
<td>1780, 1250</td>
</tr>
<tr>
<td>1b 2-Deacetyltaxine A</td>
<td>C₃₃H₄₅NO₉</td>
<td>–</td>
<td>[α]D₂₀ = –106°</td>
<td>224, 264</td>
<td>1734, 1691</td>
</tr>
<tr>
<td>1c Taxine B</td>
<td>C₃₃H₄₅NO₈</td>
<td>115</td>
<td>[α]D₂₀ = +116°</td>
<td>210, 277</td>
<td>3578, 1730</td>
</tr>
<tr>
<td>1d Isotaxine B</td>
<td>C₃₃H₄₅NO₈</td>
<td>–</td>
<td>–</td>
<td>282</td>
<td>–</td>
</tr>
</tbody>
</table>

**FIGURE 74.1** Structural formulas for taxines A.

**FIGURE 74.2** Structural formulas for taxines B.
mechanism (Gustafson et al., 2003; Baker et al., 2006). Less than 10% of the excretion is through the kidneys. Tissue distribution is extensive except for the central nervous system and testes. The elimination half-life for paclitaxel is 5–7 h (two compartment model) or 20 h (three compartment model) while the elimination half-life for docetaxel is 12 h (two compartment model) or 13 h (three compartment model). Liver insufficiency or the co-administration of compounds which modulate P450 activity may influence the activity of these antineoplastic drugs (Brown, 2003) and presumably, the activity of more acutely toxic members of the family such as taxines A and B.

### PHYSIOLOGY/MECHANISM OF ACTION

The earliest investigations of crude extracts of taxine alkaloids published in 1921 described effects that were primarily cardiovascular. When administered by the intraperitoneal or intravenous routes in rabbits and dogs, hypotension and cardiac arrest occurred in both species (Bryan-Brown, 1932). Additionally, when toxicity was severe enough to result in cardiac abnormalities, it was noted that peristaltic contractions of the gastrointestinal (GI) tract ceased.

The first extensive pharmacological research of taxines was reported by Bryan-Brown in 1932. Electrocardiographic analysis of isolated perfused hearts of rabbits and frogs revealed that crude taxine extracts gradually induced bradycardia resulting in diastolic cardiac arrest. More recent investigations have indicated that taxines depress atrioventricular (AV) conduction in a dose-dependent manner in isolated frog heart having the greatest effect on ventricular rate (Smythies et al., 1975; Tekol and Kameyama, 1987). In those studies, that effect could not be inhibited by the administration of atropine, vagotomy, or ganglionic/adrenergic blockade (Bryan-Brown, 1932; Vohora, 1972). It was thus concluded that the hypotension induced by taxine extracts was not mediated via the sympathetic or parasympathetic nervous systems, but rather by a direct action on myocardium (Vohora, 1972).

Large differences in the cardiotoxicity of taxine A and taxine B have been reported (Bauereis and Steiert, 1959; Alloatti et al., 1996). Administration of taxine B administered either in vivo or in vitro has shown that taxine B is more cardiotoxic than taxine A (Bauereis and Steiert, 1959; Alloatti et al., 1996). In the heart, taxine B causes inotropic effects while eliciting marked changes in AV conduction. In isolated, perfused guinea pig hearts, a 5 μM concentration of taxine B markedly increased AV conduction time and QRS duration (widening of the QRS interval), while 1 μM concentrations (lowest concentration used) significantly reduced heart rate (Alloatti et al., 1996). These changes led to AV conduction blocks and complete diastolic cardiac arrest. This marked increase in QRS duration (wide QRS interval) has also been reported in a case of human poisoning by yew ingestion (Matthew et al., 1993). Experimental administration of Taxus extracts intravenously to pigs also resulted in widening of QRS complexes as evaluated by electrocardiography. In those studies, sodium bicarbonate was not effective in reversing the widening of the QRS interval (Ruha et al., 2002). Additionally, taxine B causes a marked reduction in the maximum rate of depolarization of the action potential in isolated papillary muscle and thus, resembles the action of class I antiarrhythmic drugs (e.g. flecainide, procainamide, quinidine) (Bauereis and Steiert, 1959; Tekol, 1985; Alloatti et al., 1996). In contrast, taxine A has minimal effects on AV conduction time and QRS duration. Even at the highest concentration used (10 μM), taxine A induced only mild reductions in heart rate (Alloatti et al., 1996).

Taxines have lesser effects on other organs. In the few studies reported, crude taxine extracts have adverse effects on involuntary muscle, but not on voluntary muscle (Bryan-Brown, 1932; Vohora, 1972). Uterine contractions, relaxation of the intestines, and contraction of the duodenum and ileum have been noted in experimental animals dosed with yew extracts (Bryan-Brown, 1932; Vohora, 1972). More recently, Tekol and Göğüsten (1999) reported that taxine sulfate inhibits peristaltic movement in rabbit jejunum with a median inhibitory concentration (IC₅₀) of 1.86 × 10⁻³ g/ml.

Due to their instability and the lack of purified taxines A and B for experimental use, research delving into the mechanism of action of taxines has frequently involved using crude extracts of taxines from yew. However, because taxine B is present at higher concentrations and is more potent than other taxines, it is assumed that the primary adverse effects of taxines in the following investigations are primarily the result of the activity of taxine B. Investigations of taxine extracts on cardiomyocytes and axons indicated that taxines cause an increase in cytoplasmic calcium by altering both calcium and sodium channel conductances (Smythies et al., 1975; Tekol, 1985, 1991; Tekol and Kameyama, 1987). Further electrophysiological investigations demonstrated that taxines are calcium and sodium channel antagonists (Tekol and Kameyama, 1987; Tekol and Göğüsten, 1999). However, recent investigations regarding the cardioselectivity of taxines have provided more conclusive evidence that their mode of toxicity is as calcium channel antagonists (Tekol and Göğüsten, 1999). In those studies, isolated aorta, atrium, and jejunum from rabbits were used to compare the cardioselectivity of taxines to verapamil, a known calcium channel antagonist. From these experiments, Tekol and Göğüsten (1999) concluded that the mechanism of action of taxines is
primarily based on its Ca**2⁺**-channel antagonistic properties. It is likely that the toxicity of taxines in animals and humans also occurs through this same mechanism.

**TOXICITY**

With the exception of the aril, all parts of the yew plant, including the seed within the aril, contain taxine alkaloids and are extremely poisonous. One study in laboratory rodents has indicated that higher toxicity is found in stems compared to leaves (Shanker *et al*., 2002). Although maximal concentrations occur during the winter (Watt and Breyer-Brandwijk, 1962), toxic amounts of taxines remain in the plants throughout the year and are not appreciably decreased by drying (Alden *et al*., 1977). It has been reported that the cardiototoxic taxines A and B are relatively abundant in English Yew (*T. baccata*) and Japanese Yew (*T. cuspidata*), yet only minimal amounts are found in Pacific Yew (*T. brevifolia*) (Tyler, 1960; Suffness, 1995; Itokawa, 2003).

Fatal animal toxicoses have been reported in the United States, Canada, Europe, and Asia (Kingsbury, 1964; Lee *et al*., 2003). The majority of these occur in domestic livestock including cattle (Casteel and Cook, 1985; Panter *et al*., 1993), horses (Karns, 1983; Cope *et al*., 2004; Tiwary *et al*., 2005), sheep (Rae and Binnigton, 1995) and goats (Coenen and Bahrs, 1994), but have also been reported in dogs (Evans and Cook, 1991; Taksdal, 1994), a bear (Bacciarini *et al*., 1999), fallow deer in captivity (Wacker, 1983), emus (Fiedler and Perron, 1994), budgies (Shropshire *et al*., 1992), canaries (Arai *et al*., 1992), and experimentally in pigs (Ruha *et al*., 2002). It is interesting to note that yew (*Taxus baccata*) is often eaten by white-tailed deer (*Odocoileus virginianus*) in the United States without apparent adverse effects. This may be due, in part, to increased ruminal detoxification of the taxines present in the yew (Weaver and Brown, 2004). Clinical cases resulting in poisoning are often accidental and are frequently a result of livestock being unwittingly fed clippings from yew (*Taxus spp.*) bushes. Because of the difficulties in obtaining purified, stable taxines in quantities sufficient for mammalian studies, minimum lethal dose (*LD*<sub>min</sub>) values were, in the past, assessed through the oral administration of yew leaves and branches (Watt and Breyer-Brandwijk, 1962; Clarke and Clarke, 1988). Utilizing these values, and estimating that 1 g of yew leaves contains approximately 5 mg of taxines (Smythies *et al*., 1975; Tekol, 1985; Jenniskens *et al*., 1996; Tekol and Gögütüen, 1999), minimal toxic doses of taxines (mg/kg body weight) in animals can be estimated and are summarized in Table 74.2. The body weights of the animals listed are average values for adult animals only (Spector, 1956). From Table 74.2, it is evident that the minimal toxic dose of taxines varies between species. Comparatively, horses are more sensitive (*LD*<sub>min</sub> of 1.0–2.0 mg/kg) and chickens are least sensitive (*LD*<sub>min</sub> of 82.5 mg/kg) to yew toxins.

Adverse clinical signs in livestock can vary depending on the amount of yew ingested. However, in most cases of acute poisoning, animals are often found dead 24 h or less after ingestion without demonstrating abnormal behavior or adverse signs of toxicity. In subacute poisonings, which have been reported infrequently, clinical signs may include: ataxia, bradycardia, dyspnea, muscle tremors, recumbency, and convulsions leading to collapse and death (Evers and Link, 1972; Casteel and Cook, 1985; Veatch *et al*., 1988; Evans and Cook, 1991; Tekol, 1991;

<table>
<thead>
<tr>
<th>Animal</th>
<th>Estimated average body weights (kg)</th>
<th>LD&lt;sub&gt;min&lt;/sub&gt; of yew leaves (g)</th>
<th>LD&lt;sub&gt;min&lt;/sub&gt; (mg/g yew leaves/kg body weight)</th>
<th>Estimated LD&lt;sub&gt;min&lt;/sub&gt; of taxines (mg/kg body weight)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken</td>
<td>1.82</td>
<td>30</td>
<td>16.5</td>
<td>82.5</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Cow</td>
<td>250</td>
<td>500</td>
<td>2.0</td>
<td>10.0</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Dog</td>
<td>13</td>
<td>30</td>
<td>2.3</td>
<td>11.5</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Goat</td>
<td>40</td>
<td>480</td>
<td>12.0</td>
<td>60.0</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Horse</td>
<td>500</td>
<td>100-200</td>
<td>0.2-0.4</td>
<td>1.0-2.0</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Pig</td>
<td>102</td>
<td>75</td>
<td>0.7</td>
<td>3.5</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Sheep</td>
<td>40</td>
<td>100</td>
<td>2.5</td>
<td>12.5</td>
<td>Clarke and Clarke (1988)</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.025</td>
<td>NR</td>
<td>NR</td>
<td>0.5 (s.c.)</td>
<td>Tekol (1991), Tekol and Gögütüen (1999)</td>
</tr>
<tr>
<td>Rat</td>
<td>0.25</td>
<td>NR</td>
<td>NR</td>
<td>5.0 (s.c.)</td>
<td>Tekol (1991), Tekol and Gögütüen (1999)</td>
</tr>
<tr>
<td>Human</td>
<td>80</td>
<td>50-100</td>
<td>0.6-1.3</td>
<td>3.0-6.5</td>
<td>Watt and Breyer-Brandwijk (1962)</td>
</tr>
<tr>
<td>Rabbit</td>
<td>2.5</td>
<td>1.75</td>
<td>0.7</td>
<td>3.5</td>
<td>Watt and Breyer-Brandwijk (1962)</td>
</tr>
</tbody>
</table>

NR: data not reported.
s.c.: Rat LD<sub>min</sub> is based on subcutaneous dose.
*Estimated average body weights of adult animals in Table 74.2 referenced in Spector (1956).
Arai et al., 1992). In cases of deliberate yew poisoning in humans, adverse symptoms of toxicity are similar to those reported in animals. Yew ingestion results in dizziness, pupil dilation, nausea, vomiting, diffuse abdominal pain, tachycardia (initially), muscle weakness, and convulsions (Czerwew and Fischer, 1960; Fröhne and Pribilla, 1965; Schulte, 1975; Blyth, 1884). In some cases, these symptoms can proceed to bradyarrhythmia, bradypnea, diastolic cardiac standstill, or death (Fröhne and Pribilla, 1965; Schulte, 1975; Blyth, 1884; Sinn and Porterfield, 1991).

A diagnosis of yew poisoning in animals is frequently based on a history of exposure and identification of the yew (Taxus spp.) in the digestive tract. It is not uncommon that poisoning is associated with pruning bushes and then feeding the trimmings to the livestock. In some instances, it is difficult to readily obtain this information from the owners. In suspect cases, yew fragments (sometimes visible only by microscopic examination) are often found in the mouth, stomach content, rumen content, and/or small intestine. On occasion, exposure may be indicated in the history, yet gross identification of plant material is unconfirmed. This can be especially true in species that chew their food more thoroughly, such as horses. In these cases, diagnosis of taxine poisoning often requires a more detailed microscopic and/or chemical evaluation of the GI contents (Karns, 1983; Tiwary et al., 2005). Chemical analysis of GI contents (particularly stomach/rumen contents) via gas chromatography/mass spectroscopy (GC/MS), liquid chromatography/mass spectroscopy (LC/MS), or thin-layer chromatography (TLC) can be used to confirm the presence or absence of taxine alkaloids in extracts from stomach/rumen contents (Stahr et al., 1977; Kite et al., 2000; Tiwary et al., 2005). Of these techniques, GC/MS and LC/MS are the most sensitive. Currently, the only chemical standards available for these analyses are crude extracts from Taxus spp. bushes, not unlike the standards that have been used for the past 100 years.

There are no lesions at post-mortem examination which are pathognomonic in animals that have died due to yew toxicity. Indeed, neither gross nor microscopic abnormalities (with the exception of large pieces of yew leaves and stems, if they are present in the GI tract) are generally seen (Kingsbury, 1964; Alden et al., 1977; Ogden, 1988; Rooks, 1994). An exception to this is a recent case of Taxus spp. toxicosis in a horse in which ecchymotic hemorrhages were visible grossly along the endocardial surfaces of the ventricles, and microscopically, mild multifocal necrosis of the myocardium was identified in the ventricular wall and papillary muscles of the heart (Tiwary et al., 2005). In subacute poisonings, gastroenteritis may be evident, however the inflammation is probably due to an irritant oil present in the yew and not taxine (Watt and Breyer-Brandwijk, 1962; Kingsbury, 1964; Evans and Cook, 1991). Rarely, other gross changes have been reported at necropsy. These have included moderate to severe rumenitis, superficial hemorrhages in the right ventricular myocardium and right atrium, and mild focal interstitial myocarditis (Ogden, 1988; Panter et al., 1993).

**TREATMENT**

Death is frequently the first adverse clinical sign in animals that have eaten toxic amounts of yew. In these animals, treatment is unrewarding. However, in instances where known ingestion has recently occurred, it is important to remove the plant material from the GI tract and limit absorption. Rumenotomy, followed by replacement therapy with a mixture of mineral oil, electrolytes, activated charcoal, and alfalfa pellets has been effective in treating some cases of Taxus spp. poisoning in ruminants (Casteel and Cook, 1985). There is no specific antidote for taxine poisoning. Atropine or lidocaine has been suggested to be beneficial in alleviating the cardiodepressant effect of taxine (Kingsbury, 1964; Schulte, 1975). However, in experimental animal studies (Bryan-Brown, 1932; Vohora, 1972), and in human cases where the cardiac response to attempted treatment was closely monitored via electrocardiography, classic antiarrhythmic therapy has proven ineffective (Willaert et al., 2002). Additionally in humans, a variety of clinical measures such as the administration of circulatory stimulants, artificial respiration, and cardiac pacemakers have not been able to prevent death from yew intoxication (Fröhne and Pfändler, 1984).

**CONCLUSION**

Although much progress has been made during the last few decades in identifying the toxins and active diterpenoid taxanes in plants of the genus Taxus, their mechanisms of action, and their physiological effects, yew intoxication in animals remains a fairly frequent, often fatal, and largely preventable cause of livestock losses. Since the earliest indication of ingestion of toxic amounts of yew is death, and since there is no antidote and no effective treatments other than evacuation of the GI tract and prevention of absorption, education of the public as to the inadvisability of feeding yew trimmings to livestock is currently the best deterrent to Taxus spp. toxicoses.

**REFERENCES**


References

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