REVIEW

Journal of Pre-Clinical and Clinical Research, 2009, Vol 3, No 1, 001-004
www.jpccr.eu

Future perspectives of the role of Taxines derived from the Yew (*Taxus baccata*) in research and therapy

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Abstract: Yew (*Taxus baccata*) is a poisonous shrub, who´s toxic properties have been known since antiquity. Recently a molecule, paclitaxel, derived from the Yew has proved to have anticancerous properties, and now this paper raises the debate as to whether or not another molecule, Taxine B, also derived from the Yew, could be a potent new pharmacodrug. Further research in this area is now desperately required, but if positive results are found, they could change our perception of the Yew from being a toxic shrub to being the new medicinal super plant.

Key words: Yew (*Taxus baccata*), Taxine B, cardiovascular drug, malaria, potassium channels, funny channels

TAXUS BACCATA: WHAT DO WE KNOW?

Taxus baccata is a commonly occurring evergreen shrub whose poisonous features has been known since antiquity. Intoxication with yew is occurring rather commonly but inspite of this limited research has been conducted about the toxic mechanisms of the alkaloid compound Taxine B responsible for the toxicity of Yew. Research occurring in the existing literature has been focused on another alkaloid also naturally occurring in Yew, paclitaxel which is now being used as an anti cancer drug.

Components: The toxic properties associated with the Yew is caused by the alkaloid group called the taxines of which Taxine B occurs in largest amount. The taxines are however a large group consisting of at least 21 alkaloids [1] but Taxine B is the most potent of these molecules and thus suspected as have the greatest influence in terms of toxicity [2]. Taxine B is also reported to be cardiotoxic which at present is considered to be the primary toxic mode of action of the Yew. At this point in time it has not been verified in any reports as to whether some of the 21 reported alkaloids may have been formed as artefacts from the Taxine B during extraction or whether they all occur naturally in the Yew. Six of these alkaloids have been identified in heart tissue specimens from intoxicated brown bears (*Ursus arctos*) and their properties in relation to the intoxication can thus not be ruled out, at least not before it has been examined whether or not their occurrence in Yew extracts are natural or artificial. The diversity in numbers of alkaloids found in different studies gives rise to the suspicion that a number of Taxine-like alkaloids are formed during extraction due to molecular destruction, rearrangement etc. It is stated that the taxine constituents degrade easily and migration of acetyl groups and photodegradation occur readily [2]. It would thus be of great value to perform an experiment comparing results gained when using different extraction methods but the same examination settings.

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Received: 27 July 2009; accepted: 20 August 2009

Toxic effects upon the heart: Reports of the electrocardiogram (ECG) from Yew intoxicated individuals reveal an increased atrio-ventricular conduction time, longer QRS duration and absence of the P wave [3, 4]. Taxines are at present assumed to cause a rise in cytoplasmic calcium, by interfering with both calcium and sodium channels across the myocardial cell membrane. Because of this Taxines are assumed to cause suppression of the hearts depolarizing conduction system in a dose-dependent manner [4]. The reduced cardiac depolarization leads to bradycardia, arrhythmia and diastolic heart stop unaffected by the autonomic nervous system [4]. Initially a period of ventricular tachycardia is seen prior to the onset of bradycardia and it is reported that the Taxine molecule has structural similarities to digitalis [5]. In two human cases reporting mild intoxication, ventricular tachycardia and ventricular fibrillation with abnormal QRS intervals followed by bradycardia were seen, these being the characteristic findings with regard to the ECG believed to be related to Yew intoxication at the present time [5-7]. Symptoms and *post mortem* findings are related to the cardiac effects of the Taxines including hypotension, congestion and shock.

Reported doses of importance: Many animal species have been reported to have accidentally died from Yew intoxication over the years, and this has given rise to reports of lethal doses of ingested Yew material [4]. However there is a great difference between the amount of Taxines in the Yew ingested, amount of Taxines absorbed and Taxine concentration required to produce a fatal cardiac arrest, as shown in a recent report on two fatally intoxicated brown bears [8]. This is the first report in which the tissue concentration in the heart of fatally intoxicated individuals has been determined. It is however difficult to determine amount Taxines absorbed as this may be affected by many factors.

Former physiological studies on heart effects: Formerly experiments have been conducted on isolated frog heart, single isolated ventricular cells from guinea pigs and isolated aorta, atrium and jejunum preparations of rabbits [9-11]. An extract of taxines was converted to sulphate salts and a LD_{50} was determined on mice (s.c.) – this being 13.1 mg/kg. In the isolated frog heart atrial and ventricular rate were slowed

dose-dependently but the effect was most prominent in the ventricle and atrio-ventricular conduction [9]. This report also showed Ca^{2+} antagonizing properties [9] consistent with later findings [3] who classified the Taxine B as a class 1 antiarrythmic drug. Another study showed the protective effect of taxine on experimental myocardial damage in rats [12], resembling other calcium channel blockers. In the single ventricular cells from guinea pigs, membrane currents were studied and the authors found that the drug inhibited both the sodium and calcium currents in a similar way to antiarrythmic drugs [10]. A partial recovery from the effects of taxine was possible but this study also showed inconsistent effects on the outward potassium current [10]. Finally, Yew extracts have been reported to have been used about a thousand years ago as a means of setting the heart at ease [13].

ECG and potassium: At present no records are found describing recordings of the entire course of intoxication. Reports are found stating increased atrio-ventricular conduction time longer duration of the QRS complex and absent P waves on ECG [4, 14]. As the P wave has been reported to be absent during Yew intoxication, interaction with potassium channels has been suspected. An absent P wave indicates atrial depolarization [15]. The hyperkalemic state, that is to say serum K^+ concentrations above 7 mEq/L, cause an absence of the P wave [16]. Thus, as the P wave is absent in Yew intoxicated individuals it seems reasonable to suspect Taxine interference with potassium ion channels. This is interesting for several reasons. If there are actions upon potassium channels this effect may be specifically performed on the so called "funny channels", which are special ion channels situated in the sinoatrialnode cells in the heart, and as such this could account for the greater toxic potential of Taxines in the heart compared to other tissue types. Second, if potassium channels are affected by the Taxine molecule, this would make the Taxines interesting in relation to the search for anti malarial drugs. A property of modulating potassium ion channels is essential in an anti malarial drug since research has showed that the *Plasmodium falciparum* K^+ channel is a potential drug target [17, 18]. At present the downside effects of the Taxines are the ones known, and of course further examination of the Taxines are required. Should they prove to possess these potassium ion channel modulating properties, it will make Taxines obvious candidates in the search for anti malarial drugs. The Taxine molecule could then be modulated to find a molecule with the precise desired potassium ion channel modulating properties, but with a better effect versus side effect profile. Of course if the properties of Taxine can be better understood, the reported similarity with digitalis would constitute an opportunity to develop a modified Taxine molecule useful in failing heart patients, as it could then be a pharmacodrug. Moreover, if this drug could be shown to bind in the blood, and thereby facilitate a slow release system, this would be the most favorable scenario. It has been suggested that it is the combined effect of the taxine alkaloids and their corresponding cinnamates, that are able to reduce coronary flow in the heart and exitability [3]. Cinnamates are molecules derived from degradation of taxines [2]. This underlines the presence of the possibility for modulating a taxine molecule to possess desired properties. However, it is important to understand the function of Ca^{2+} influx on K^+ balance in cardiac cells during the Yew intoxication phase, and for this, further examination is required since the role of K^+ ion channels remains uncertain owing to inconclusive results. Finally a report occurs about the use of Yew in antiquity: "So it was reported to have antimalarial, antirheumatic, antiepileptic and aperients applications" [13]. This is interesting in the context of antimalarial research.

Funny channels: Funny channels are situated on the pacemaker cells of the sino-atrial node in the mammalian heart and responsible for the so-called funny current I_f. Funny currents are inward, are activated on hyperpolarization, and have unusually slow kinetics [19]. They are carried by both sodium and potassium ions, which in itself is an unusual feature and it plays a central role in the generation of diastolic depolarization. Funny currents are also found in other cell types such as a large variety of neurons and smooth muscle cells [19]. Combined with the existing knowledge of Taxine B this may be the explanation for the diverse symptoms seen with Yew intoxication, e.g. lack of coordination, muscle trembling, hanging lips and an effect on isolated jejunum from rabbits [11, 14].

Histology: Histological changes in the heart have been reported in an intoxicated horse, where contraction band necrosis was found [14]. In a study with two brown bears similar contraction band necroses were found [8]. To the best of current knowledge these are the only two reports on histological examination of heart tissue following Yew intoxication, and more now needs to be learnt about this phenomenon.

ADME: Very little is known about the absorption, distribution, metabolism and excretion of Yew related alkaloids. Very few citations or reports are to be found on the subject, and those that do exist state that Taxines are rapidly absorbed from the gastrointestinal tract, metabolized through conjugation in the liver, and excretion, at least in herbivores, occurs as benzoe acid and hippuric acid by the kidneys [20, 21], however, some degree of critisism should be levelled at these reports. Also one report mentions that the half-life of Taxine is unknown [6], while another report states a great similarity in amount absorbed between taxines ingested peroral and those administered *via* an intraperitoneal injection [22]. Broad acceptance exists regarding the idea that the gastrointestinal irritation seen in Yew intoxication is caused by a long list of compounds in Yew, such as nitriles, ephedrin and volatile oils [23]. An experiment with rats treated with a Yew extract shows elevated levels of alkaline phosphatase and transaminase, indicating a toxic effect on the liver. This experiment also finds a disturbance of erythropoeitic tissue [24].

SO WHAT WOULD IT TAKE?

Some research has been made on blood levels with positive results but it is not very likely that a snap test for taxines will be developed even though the possibility may exist. Blood analysis is a further possibility to be investigated, as many veterinarians and medicals usually draw blood from their patients. However they also frequently do an ECG and this is the main scope for these requested studies. Therefore a guideline should be made as to what symptoms are seen at various stages of the intoxication and how the reaction should/could develop. Attempts should be made to set-up a treatment guideline when an understanding of the intoxication stages has been obtained. Treatment should take into account the current stage of intoxication and the following stage as former

reports show limited effect of treatment due to changes in the course of intoxication [7].

Thorough investigation is needed regarding symptoms, ECG, properties of the Taxine molecule as to ion channel level and different channel types, different cell types being investigated and ADME. Histology can be used to confirm the location of the primary mode of action by making sections in different parts of the heart, such as the right and left atrium and the right and left ventricle, supplemented by sections of the atrio-ventricular node and around the Purkinje fibres. All the pathological / histological changes could then be reported systemically and predilection areas, if any, of the taxines thus determined. Primary lesions expected in the heart, based on current knowledge, would include contraction band necrosis [8, 14].

RESULTS AND PERSPECTIVES

If these many experiments were conducted and of course dependent on the findings and results, they should provide information to form basis for development of a guideline on how to treat Yew intoxicated individuals. Furthermore the ECG measurements could provide data that may give more information as to the mode of action of Taxines *in situ*. When the exact course of the ECG during intoxication has been determined, new information useful for the cellular examination may be deduced. Overall it should be said that the perspectives on the future use and development of Taxine derived drugs depends on the outcome of future studies. However if the results we anticipate are found, there are a great many possibilities.

Heart failure is a common, costly, disabling and deadly condition. In general it is assumed that of adults over the age of 65 the incidence of heart failure is 6-10% of the population and progressive disease is associated with an overall 10% annual mortality rate. It is a disease associated with reduced physical and mental health resulting in decreased quality of life [25]. If the aforementioned experiments give positive results and a new pharmaco drug is developed, this would have a tremendous impact on these people and their quality of life. It is a very amiable goal in itself to perform studies with far reaching consequences. Furthermore, some attention has been directed at the dangers of novel drugs producing long QT in patients, which is a most unwanted side effect in a drug. Methods for monitoring the effect of a drug on potassium channels and monitoring for long QT intervals could be developed by combining knowledge on zebra fish and Taxine. The use of Taxine B or one of the related alkaloids may prove useful in setting a standard for evaluation of new drugs, as it has already been shown to cause a longer QRS duration and through further understanding of this mechanism a "Gold" standard level may be arrived at.

With respect to malaria it is known to be mans greatest killer causing about one-three million deaths annually. Malaria affected persons are commonly poor and malaria is thus associated with poverty but also causing poverty and as such a hindrance for economic development [26]. Resistance to some of the existing malaria drugs has been reported and this further stresses the need for novel drug development. As mentioned above, a few statements in the literature may give an indication that one of the Taxines from Yew holds potential in respect to this.

Should Yew prove to be the wonder plant of our generation, considerations should be made as to whether it would be reasonable to exploit this knowledge on gene modifying organisms. The Yew could be modified to express the gene codon responsible for production of the Taxine alkaloid desired for the new drugs, if the alkaloid can not be produced synthetically. In relation to the discovery of the anticancer drug, paclitaxel, some research has been made on the nature of Yew in the context of optimizing production of the desired molecule. Knowledge from this research could be applied in the production of the Taxine alkaloid.

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