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A tribute to the memory of the illustrious maestro and academic Dr. Rafael Méndez Martínez, pioneer in the pharmacological studies of digitalis and digitalis glycosides

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Abstract

Since the end of the XVIII century, digitalis glycosides were employed in heart failure. They were considered initially as diuretics and later as cardiotonic agents or as positive inotropics. At the present time there are varied groups of positive inotropic agents, which have a beneficial action on the failing human myocardium. For example, the beta adrenergics, the phosphodiesterase III inhibitors such as milrinone, or the sensibilizers of myocardial proteins to Ca^{++} such as levosimendan and omecamtiv mecarbil. However, following the opinion of distinguished cardiologists, in the case of heart failure associated to atrial fibrillation, digitalis cannot be substituted. (Gac Med Mex. 2015;151:614-8)

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Digitalis

In the 16th century, during the evolution of knowledge on medicinal botany, most valuable, history-making works were published: *De Historia stirpium,* by the German Leonhart Fuchs[1], the catalogues by Charles de l'Ecluse or Hieronymus Bock, the descriptions of American medicinal plants by the Aztec physician Martín de la Cruz (1552), some texts written by Dr. Francisco Hernández, protophysician of the New Spain or by the Sevillian physician Nicolás Monardes, etc. However, as Laín Entralgo pointed out[2], the main taxonomic concepts of that age remained faithful to those by Aristotle and Theophrastus. Only with Swiss physician and naturalist Konrad von Gessner (1516-1565), modern taxonomy began to consolidate.

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Digitalis was first described in the *Nuevo Herbario* (New Herbarium) (1543), by the above-mentioned Dr. Fuchs (1501-1566)[3], as described in Levy's publication[4]; it appears on Fuchs' book chapter 345 with the title: "Von Finger-Hutkraut" ("On the plant with flowers shaped as a thimble", i.e., *Finger-Hut*[5]) (Fig. 1). The author had named it *Digitalis* in the Latin edition of his herbarium, where he distinguished the purple and yellow varieties, according to the color of the flowers. In addition, he described *Digitalis purpurea's* visceral decongestant effect[3]. In turn, Hieronymus Bock, a physician and botanist from Hombach, reproduced in 1546 one of the first images of the digitalis plant on his book *Kräuterbuch,* printed in 1595 in Strasbourg.

All this we had already described in a previous publication, which appeared some years ago in the *Revista de la Academia Nacional de Medicina de México*[6].

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Figure 1. *Drawing of a D. purpurea plant.*

Therapeutics with digitalis

Digitalis irruption in clinical therapeutics is described in the classical monograph by Withering[7] (1721-1791), a physician at Birmingham General Hospital and member, together with Joseph Priestley, James Watt, Erasmus Darwin and others, of the Lunar Society, a scientific gathering that met every month on full-moon nights. This monograph addresses the early uses of digitalis, according to a communication of Dr. Stokes from Stourbridge. The monograph states, among other things, that an Orléans physician, Dr. Salerne, had made experimental observations on intoxication with digitalis in turkeys, which were the subject of a report of the National Academy of Sciences in 1748.

Digitalis glycosides

In 1868, the French pharmacist Claude Nativelle, after several attempts, obtained pure crystallized digitalin[8], which practically corresponds to the digitoxin isolated in 1874 by Oswald Schmiedeberg (1838-1929)[9]. Towards the end of the 19th century, Houghton initiated biological dosing of digitalis compounds in the frog[10]. This way, the rational use of digitalis compounds started in Western Europe, in the form of Nativelle's digitalin 10% alcoholic tincture. But only over the course of the 20th century has it been possible to isolate other *D. purpurea* active ingredients: gitalin and gitoxin[11]. In addition, Swiss chemist Stoll[12] discovered, on *Digitalis lanata's* leaves, two glycosides not present in *D. purpurea:* lanatoside C and its derivative digoxin[12]. At that time, all digitalis glycosides were shown to stem from the steroid or cyclopentanoperhydrophenanthrene nucleus, just as cholesterol, biliary acids, sex hormones, adrenocortical hormones and vitamin D do[14].

With regard to strophanthus derivatives, botanist Kirk, a member of David Livingstone's expedition along the Zambese River (1858-1864), noted the cardiac action of *Strophanthus,* the venom of which was infused by natives to their arrows. On the other hand, Fraser[15], in the 1869-1872 period, studied strophanthus properties and isolated the first amorphous glycoside. Years later (1888), Arnaud[16] managed to isolate ouabain, also known as strophanthin because it was obtained from *Strophanthus gratus.* Towards the end of 19th century and early 20th century, K-strophanthin[17] and digitalis[18] intravenous administration was promoted. Withering described 163 cases where he administered a digitalis leaves' brew and added 48 cases more belonging other physicians' practice, his correspondents. Indications for the use of this drug were essentially anasarca and ascites, and for this reason the English investigator attributed it a diuretic effect, even when he recognized that the drug had "an action on the heart's movement, not observed with other drugs". The pharmacologist Rafael Méndez believed that "probably the author referred to cases of atrial fibrilation, where digitalis slowed the pulse rate"[19].

On the other hand, French physician F. T. Bidault de Villiers, in an 1805 publication[20], already recommended the use of digitalis tincture due to its effects on the heart and diuresis. But digitalis therapeutics found certain opposition by some great Gallic clinicians, such as Corvisart and his disciple Laënnec. The former, in article V of the *Corollaires,* in his treatise *Essai sur les maladies et les lésions organiques du coeur et des gros vaisseau,* dedicated to Emperor Napoleon I[21], quotes the *Scilla,* but he doesn't mention digitalis at all. The latter, didn't consider digitalis action to be reliable. In fact, in volume II of his 1826 treatise[26], there is a chapter fully addressing the treatment of heart failure where the following can be read: "Digitalis is widely used in our times for the treatment of heart diseases, in agreement with general opinion that, in addition to its diuretic effect, it exerts a sedative action on the

heart as well. I confess I have never found such an action to be either evident or constant, even when elevated doses were administered, able to cause vomiting and vertigo… Digitalis therapy, therefore, cannot be considered an efficacious measure in the treatment of heart hypertrophy". Conversely, Dr. Jean Bouillaud, in volume II of his *Traité clinique des maladies du coeur* (1835)[23], recommended digitalis for the treatment of chronic endocarditis (p. 235) and cardiac hypertrophy (p. 461), and defined it as the true "opium of the heart". Additionally, in a footnote, he criticised Dr. Laënnec's attitude towards the "bonne digitale qui ralenti le coeur".

Digitalis in Mexico

With regard to the introduction of digitalis in Mexico, it should be mentioned that in 1821, in the capital city of the country, a brief treatise by Charles-Louis Cadet de Gassicourt was brought to light, in the Spanish translation made by Nicolás Molero. It was the *Formulario magistral y memorial farmacéutico* (Magistral formulary and pharmaceutical memoirs)[24], where the use of digitalis infusion and tincture was recommended against anasarca. The first graduation thesis on a cardiologic subject, developed in the National School of Medicine by Dr. Mariano Carrillo, was published in 1870[25]. It was followed in 1872 by the first thesis on digitalis, where Nativelle's digitalin was introduced[26], described in detail in the *Gaceta Médica de México.* On the other hand, volume III index (1890) of *El Estudio* journal, official publication of the National Medical Institute, includes full notes concerning "Digitalis in pediatrics" (p. 45) and "Digitalis and digitalis compounds" (p. 202). Professor Ignacio Chávez completed his medicine career in May 1920 in the Universidad Nacional de México Faculty of Medicine with a dissertation on his professional thesis entitled: *La digitalina a pequeñas dosis en el tratamiento de las cardiopatías* (Low-dose digitalin in the treatment of heart diseases)[27]. Some other thesis on the subject is quoted in a book by Francisco Fernández del Castillo (1961)[28] and in the Catalogue of Theses on Medicine of the 19th Century[29].

In our institute, Professor Ignacio Chávez Sánchez used to employ a strophanthus derivative, ouabain, by intravenous route[14]. In the past years, it was widely used, as well as lanatoside C (cedilanid). Today, digoxin is used by oral route and, in certain cases, intravenously, since both ouabain and lanatoside C are unavailable. Digoxin therapeutic plasma concentration is considered to range from 1 to 7 nM.

Digitalis actions

The serious foundation of investigations on the bioelectrical properties of cardiac tissues was established in the 18th century in publications by Albrecht von Haller[30] and Felice Fontana about animal tissues' irritability. One century later, in the classical work by Etienne Jules Marey[31], the relationship of the ventricular myocardium refractory period with the phases of the cardiac cycle was established. This was the first decisive step for the later understanding of the myocardial excitability recovery curve. In the 19th century, digitalis compounds effects on the properties of the cardiac muscle were tried to be elucidated. Thus, in 1855, Edme Felix Alfred Vulpian described the ventricular myocardium contracture in the frog by intoxication with digitalis[32]. Later, in 1897, Cushny[33] managed to demonstrate the action of digitalis on atrial and ventricular contractility in the heart of the dog in situ. With regard to the positive inotropic action of digitalis glycosides, and in particular of ouabain, which some try to deny or minimize, some experimental studies conducted some time ago in the pharmacology and electrocardiography laboratories of our institute can be quoted. These have clearly demonstrated that digitalis compounds increase the magnitude of the ventricular myocardium contraction in the canine heart in situ.

Pleiotropic actions

In addition to their effects on myocardial contractility, useful in the treatment of heart failure, digitalis compounds induce other actions that can be considered as pleiotropic of therapeutic nature. These pharmacological characteristics include those related to their pharmacokinetic differences, their actions on other physiological properties of the heart, such as the prologation of the atrioventricular (AV) node refractory period, the atrial myocardium refractory period shortening-dependent antiarhythmic nature. Recently, an effect on cell development, dependent on extracellular space concentration of digitalis compounds, was added.

Pharmacokinetic differences

There are pharmacokinetic differences across several digitalis compounds, which impact especially on bioavailability and duration of action of their therapeutic effects. From a qualitative point of view, digitalis glycosides exert the same action. What makes them different to each other is the time of onset and duration

of their effect. *D. purpurea's* active substances have slow action and elimination, such as digitoxin and Nativelle's digitalin, whose peak effect is reached at between 8 and 10 h. When used in chronic heart failure, digitalization is reached at 24-48 h. On the other hand, ouabain and K-strophanthin are characterized by rapid action and elimination, with a peak effect at 45-60 min.

Prolongation of AV node refractory period

By the mid-20th century, the physiologist Arturo Rosenblueth[34] defined, in Mexico, the concept of functional refractory period of the nerve: it is the shortest interval between two conducted responses. The behavior of this parameter in cardiac tissues was studied under normal conditions[35] and under the action of digitalis glycosides. Digitalis glycosides were shown to prolong the AV node refractory period by means of a peripheral anti-adrenergic action and stimulation of the vagal nucleus, located on the floor of the fourth ventricle of the medulla oblongata[36-38]. This pharmacological feature establishes the pharmacodynamical bases of digitalis compounds in atrial fibrilation-associated hearth failure and supraventricular paroxysmal tachycardia. It also supports the concept of digitalis compounds and b-adrenergic receptor blocking agents' co-administration usefulness in atrial fibrilation[39].

Digitalis compounds antiarrhythmic activity dependent on their interaction with adenosine

Experimental studies by the Pharmacology Department of the National Institute of Cardiology have described an adenosine-releasing component in the atrial myocardium, which is dependent on digitalis action[40,41], and have demonstrated that digitalis compounds act in a different manner on the contractile atrial myocardium and the AV-conduction-specific tissue: they shorten the refractory period in the former and prolong it in the latter with participation of an adenylic compound, adenosine[40,41]. This action explains, at least in part, the conversion of atrial flutter into atrial fibrilation, which immediately shifts from recent establishment to sinus rhythm.

Digitalis compounds action on cell development

Studies by the National Institute of Cardiology Pharmacology Department, aiming at apoptotic myocardial induction by digitalis intoxication, led to the finding that cell development is modulated by the concentration of the digitalis compound employed[42]. In cervical cancer Henrietta Lacks (HeLa) cell cultures, the effect of four digitalis compounds (ouabain, strophanthidin, digoxin and digoxigenin) on cell proliferation and death was studied. Concentrations of the employed digitalis compounds lower than 10 nM increased HeLa-cells proliferation. Higher concentrations increased apoptotic cell death and were associated with canges in cell nuclei morphology, DNA degradation, cytochrome C mitochondrial release and caspases 9 and 3 proteolytic processing. These results have raised interest of investigators in the area of anti-cancer therapy and have been referred to in nearly 40 published works on the subject. For example, two titles are quoted: "Digitalis, a targeted therapy for cancer?" and "Assembling the puzzle of anti-cancer mechanisms triggered by cardiac glycosides"[44].

Synthetic digitalis compounds

Accurate definition of digitalis compounds chemical structure, initiated since mid-19th century, has enabled the conduction of some studies on the relationship between their chemical structure and their actions on the heart. These studies have led to the design of modifications in the digitalis chemical structure aiming to obtain more efficacious compounds with higher safety margins. Some positive results have been obtained. Different modifications have been practiced in the digitoxin steroid nucleus, such as rotation of the lactone ring point of insertion towards C7 of the steroid ring, which has resulted in a digitalis derivative known as actodigin[45] that has an extraordinary quick onset of action in heart failure, supraventricular paroxysmal tachycardia and atrial flutter, as well as a safety margin three to five-fold higher than digitoxin[45]. This finding has led to the proposal of two potential digitalis-derivatives cell receptors, one for their positive inotropic activity and other for their toxic actions. Rapid dissipation of toxic effects has also been achieved in actodigin[46].

Endogenous digitalis compounds

On the other hand, it should be mentioned that, for years, the existence of endogenous factors with digitalis-like action has been noted[47-49]. There are elements in favor of the belief that the physiological action can be attributed to these circulating factors.

The study of digitalis glycosides is not exhausted. With regard to digitalis intoxication, we know that it can

be prevented with a hyposodic and hyperpotassic nutritional regimen, which is generally not mentioned in modern multi-center studies and in very large trials. With regard to the marked digitalis intoxication, there is broad clinical experience on anti-digitalis monoclonal antibodies administration – digitalis gycosides are considered to be haptens –, which can revert serious states of intoxication in few moments[50].

On the other hand, it should be taken into account that pyridine-derived new positive inotropic agents, such as milrinone and others[51-53], appear not to provide real clinical benefits in mid- and long-term treatments, and angiotensin-converting enzyme (ACE) inhibitors[54] fail to control chronic heart failure on their own, even when not associated with atrial fibrilation.

Conclusions

It seems justified to conclude these brief notes with a statement made by the unforgettable pharmacologist Rafael Méndez[19]: "In case of heart failure associated with atrial fibrilation, digitalis is irreplaceable". Perhaps now we might add that digitalis compounds are also useful in the treatment of chronic heart failure not associated with such arrhythmia.

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