British Journal of Medicine & Medical Research
8(5): 477-484, 2015, Article no.BJMMR.2015.470
ISSN: 2231-0614

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Ouabain and Endogenous Ouabain -Dr. Jekyll and Mr. Hyde of Cardiac Glycosides?

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/17042
Editor(s):
(1) Oswin Grollmuss, Head of Department of Pediatric and Adult Resuscitation Congenital Heart of Centre Chirurgical Marie Lannelongue, University Paris XI, France.
Reviewers:
(1) Anonymous, USA.
(2) Hassan Ali Abd Elwahed, Family Medicine, Suez Canal University, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1117&id=12&aid=9125

Mini-review Article

Received 24th February 2015
Accepted 7th April 2015
Published 5th May 2015

ABSTRACT

In current research reports several disease states are claimed to be associated with elevated levels of endogenous ouabain. These include hypertension, cardiac enlargement, cardiac and renal failure, and a variety of terminal disorders. It has been suggested that endogenous ouabain should be considered as a major contributor to increased blood pressure and overall cardiovascular risk. These hypotheses stand in stark contrast to decades of clinical experiences with ouabain in humans, which indicate that plant-derived ouabain is effective in treating heart failure. In patients with hypertension ouabain lowers blood pressure. These conclusive clinical experiences refute the hypothesis that ouabain in humans is a major contributor to increased blood pressure and overall cardiovascular risk. The pronounced dependence of the ouabain effects on the dose, the state of the autonomic nervous system and species-specific characteristics in pharmacokinetics may explain many of the conflicting research results that have been published on experiments with ouabain. Rodents have different sensitivities to cardiac glycosides than humans. Pharmacokinetics of cardiac glycosides in rodents are also different from humans. Therefore, caution is advised when extrapolating experimental results in rodents to humans. The mutually exclusive effects of ouabain and the endogenous inhibitor of the Na/K-ATPase observed in mammalian tissues do not support the hypothesis that this inhibitor is identical with ouabain, but favour the interpretation that De Wardener's "third factor" is something different, which also reacts to ouabain antibodies.

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Keywords: Cardiovascular diseases; endogenous ouabain; hypertension; ouabain.

1. INTRODUCTION

In his famous novella “The Strange Case of Dr. Jekyll and Mr. Hyde“ Robert Louis Stevenson tells the story of a London lawyer who investigates strange occurrences between his friend, Dr. Henry Jekyll and the evil Edward Hyde. In common language "Jekyll and Hyde" has become a synonym for "split personality", referred to in psychiatry as dissociative identity disorder, where within the same body there exists more than one distinct personality. According to some recent publications on endogenous ouabain such a “split personality” also has to be attributed to the cardiac glycoside ouabain. Plant-derived ouabain has successfully been used for more than a century to treat heart diseases and hypertension [1]. In contrast, endogenous ouabain is claimed to be a major contributor to hypertension and overall cardiovascular risk [2]. Hence, we are dealing with mutually exclusive therapeutic effects of the same molecule.

2. MR. HYDE

Investigators studying hypertension have long proposed that an endogenous ligand inhibits the Na/K-ATPase activity in vascular tissue, causing vasoconstriction and an increase in blood pressure. It has been suggested that ouabain might be this endogenous ligand. However, the identity of plant-derived ouabain with endogenous ouabain (EO) and the presence of this steroid in mammalian tissues are still controversial [2,3]. This controversy notwithstanding, in humans levels of endogenous ouabain have been correlated with blood pressure and various disease states. Specific instances of adverse outcomes associated with elevated endogenous ouabain include hypertension, cardiac enlargement, cardiac and renal failure, and a variety of terminal disorders [4]. For some inexplicable reason the extensive literature on clinical experience with ouabain in patients is not cited in such publications on endogenous ouabain. Speculative mechanisms have been proposed by which EO might induce hypertension. Accordingly EO should be considered as a major contributor to increased blood pressure and overall cardiovascular risk [5]. It is asserted, that it is difficult *“to dismiss the striking correlation between the highest plasma EO levels and the worst morbidity and mortality statistics in patients with heart failure and related cardiovascular diseases.”* [2].

Based on the hypothesis that ouabain causes hypertension ouabain antagonists have been tested in the treatment of hypertension. A clinical phase II study with an appropriate drug candidate (Rostafuroxin) has failed to support the thesis that ouabain antagonists generally lower blood pressure in man. In five double-blind cross-over studies Rostafuroxin did not reduce blood pressure at any dose [6].

Experimental animal studies on the effect of ouabain on blood pressure have yielded conflicting results [reviewed in reference 7]. Especially information regarding the postulated hypertensive effect of the long-term administration of ouabain is inconsistent. Genetic differences of different rat strains influence the blood pressure effects of ouabain in rats [8]. A recent study again demonstrates that long-term administration of exogenous ouabain does not cause hypertension in male wistar rats [7]. Molecular remodelling in mesenteric arteries that could support the development of hypertension was not evident. Instead, the plasma level of vasodilatory calcitonin gene-related peptide significantly rose in the ouabain-treated rats. Several parameters indicate that the activity of the sympathetic nervous system was not increased. Instead, indices of cardiac vagal nerve activity were elevated. In dogs ouabain evokes reflex coronary vasodilation by stimulating cardiac receptors [9]. This reflex response is mediated by activating cholinergic vasodilator fibers and inhibiting sympathetic vasoconstrictor fibers. These results are in agreement with the clinical experience where vagomimetic and sympatholytic effects characterize the therapeutic effects of ouabain. These results further substantiate the documented experience, that ouabain in therapeutic concentrations in clinical practice does not increase blood pressure.

3. DR. JEKYLL

The Strophanthus glycosides ouabain (referred to as g-Strophanthin in German) and k-Strophanthin have been widely used in Europe and Latin-American countries to treat heart diseases. The database of the German Institute for Medical Documentation and Information records in addition to several solutions for intravenous administration over 20 orally administered ouabain preparations that were used in Germany after 1950. Thus, millions of patients have been treated with ouabain.

The therapeutic profile and the disease profiles for which the use of Strophanthus glycosides is appropriate are documented in many reports on clinical experiences and have been summarized in monographs and reviews, preferably in the German literature [1]. Ouabain has been used preferentially for the treatment of ischemic heart diseases like angina pectoris and coronary heart disease while digoxin causes a worsening of symptoms here and is therefore contra-indicated. Based on treatment of more than 1.000 patients with IV-administered ouabain Chavez [10] confirms the experiences documented in the German literature by emphasizing that ouabain *"is the heroic remedy for the acute phenomena of failure of the left ventricle, as it is also the remedy of choice for chronic failure of the left side of the heart in persons suffering from coronary arteriosclerosis, long established hypertension and aortitis. "It is generally accepted that in human beings nontoxic doses either of digitalis or of ouabain are not hypertensive."*

Ouabain and digoxin in high enough concentrations both increase blood pressure [11]. As noted by Chavez, in therapeutic concentrations no such effects are observed. In accordance with the experiences described by Chavez, Edens [12] reported that Strophanthus glycosides are particularly suitable for heart patients with high blood pressure. The sensitivities of patients for ouabain are different. Ouabain lowers blood pressure in hypertensives but has no influence on blood pressure in patients with healthy hearts [13]. Pidgeon et al. [14] have confirmed this observation. Intravenous injection of ouabain into healthy human volunteers did not raise blood pressure, nor did it affect renal blood flow, glomerular filtration rate, hourly urine volume, or Na+ and K+ excretion.

Altmann reported very positive clinical experiences with perlingually administered ouabain solution in more than 50 patients with different degrees of heart failure [15]. None of the patients experienced an increase in blood pressure. It is emphasized that ouabain treatment is preferred for patients with hypertension.

Kracke reported effects of orally administered ouabain on patients with heart disease and angina pectoris [16]. 33 out of 40 patients became free of complaints upon treatment with ouabain. Amongst the 40 patients, 31 suffered from hypertension. In 24 out of the 31 hypertensives, ouabain lowered the blood pressure (by 40 mm Hg systolic, 15 mm Hg diastolic); in 7 patients with hypertension the blood pressure remained unchanged. There was no increase in blood pressure in any patient.

W. Rothmund documented the effects of oral ouabain on 389 heart patients with hypertension [17]. The blood pressure of all patients was normalized by ouabain, with the exception of two suffering from severe hypertension.

These clinical findings are also in accordance with a study by Mason and Braunwald who observed that in contrast to healthy volunteers in patients with congestive heart failure ouabain augmented forearm blood flow, while mean arterial pressure remained essentially stable. Forearm vascular resistance declined [18].

The extensive clinical experiences with ouabain are complemented by experimental in-vitro and in-vivo studies that indicate cardio protective effects. Ouabain prevents hypertrophy of the heart and the adrenal cortex in rats exposed to hypoxia induced by extreme exercise [19,20]. In rat and rabbit hearts short exposure to a low concentration of ouabain protects the heart against ischemia/reperfusion injury [21,22]. In addition, experimental results indicate promising effects of ouabain in cystic fibrosis [23,24], cancer [25,26], and protection of kidney development from adverse effects of malnutrition [27,28].

Thus, decades of clinical experience and experimental findings refute the assertion that ouabain is *"a major contributor to increased blood pressure and overall cardiovascular risk"* [5].

4. MODE OF ACTIONS OF OUABAIN

Effects on the sodium pump are the major focus of experimental ouabain research. In high concentration ouabain inhibits the sodium pump, in therapeutic concentration ouabain stimulates the sodium pump. In addition, the ouabain–Na/K-ATPase interaction induces the assembly of multiple protein complexes into functional microdomains that activate diverse signaling pathways [29].

Cardiac glycosides modulate the autonomous nervous system [30]. In fact, a tabulation of the therapeutic and toxic effects of cardiac glycosides is strikingly similar to a tabulation of the combined effects of acetylcholine and

epinephrine [31,32]. Lipophilic cardiac glycosides have greater sympathomimetic effects; hydrophilic cardiac glycosides have greater vagomimetic effects. For digoxin as a strong inotrope there is evidence of only weak modulation of the autonomic nervous system. In Strophanthus derivatives the modulation of the autonomic nervous system prevails over weak inotropic effects.

Ouabain modulates cardiac metabolism. It stimulates glycogen synthesis and increases lactate utilization by the myocardium. Ouabain reduces catecholamine concentration in healthy volunteers, promotes the secretion of insulin, induces release of acetylcholine from synaptosomes and potentiates the stimulation of glucose metabolism by insulin and acetylcholine. In short, ouabain provides the starving heart in heart failure with life saving energy [reviewed in [33]. Just like ischemic preconditioning ouabain activates the reperfusion injury salvage kinase pathway [21] and provides protection against hypoxia and ischemia [34]. In dogs application of ouabain increases resistance to hypoxia [35,36] and eliminates cardiac insufficiency induced by ischemia [37].

Ouabain and digitalis derivatives unfold their effects in different cellular spaces. Digitalis derivatives penetrate into the cell interior to exert their effects, whereas ouabain develops its effect in the extracellular space. Löhr et al. [38] showed by autoradiography that [3H]-ouabain binds only to the extracellular side of the plasma membrane of myocardial cells, whereas digoxin penetrates into the cell interior. Several research groups have subsequently identified direct interaction of cardiotonic steroids with the intracellular ryanodine receptors. Núnez and Fernández report a striking difference: only digoxin and digitoxin penetrate into the cell interior and bind to the ryanodine receptor and thus induce release of Ca^{2+} in the sarcoplasmatic reticulum. In accordance with Löhr's autoradiography results, ouabain does not enter the cell interior but remains in the extra cellular space [39].

In addition, the lipophilic character of digitoxin and digoxin enables these molecules to form calcium-conductance pathways in cultured cells and cation-selective calcium channels in planar lipid bilayers in-vitro. Based on these findings Arispe et al. [40] postulate that intrinsic calcium channel activity constitutes a biologically important, calcium-dependent toxicity mechanism for digitoxin and related lipophilic glycosides. Ouabain is hydrophilic and hence cannot form calcium channels in lipid membranes.

5. CARDIAC GLYCOSIDES ARE HORMETIC SUBSTANCES

Cardiac glycosides' effects have unique dose-response relationships characterized by opposing effects from low versus high serum concentration. Cardiac glycosides are prototypical examples of hormetic substances. In high concentration ouabain inhibits the sodium pump, in therapeutic concentration ouabain stimulates the sodium pump. While low doses of digitalis inhibit sympathetic outflow, large digitalis doses have been demonstrated in animal studies to excite the central nervous system, resulting in enhanced sympathetic outflow and cardiac arrhythmias [41]. Low doses of ouabain inhibit spontaneous sympathetic activity in the preganglionic sympathetic nerves to the cat heart. Larger doses of ouabain cause an increase in sympathetic nerve activity and development of ventricular tachycardia [42]. Low concentrations of ouabain induce proliferation of several cell types, whereas higher concentrations lead to apoptosis [43,44].

Digoxin at low doses improves the neurohormonal profile in patients with heart failure. Dose increases have sympathomimetic effects [45,46]. Low doses of lanatosid C improve oxygen deficiency tolerance in angina pectoris patients; high doses decrease the tolerance considerably [47,48]. The hormetic dose-response curves of the glycosides, although matching in principle, have crucial concentration differences. In therapeutic concentrations digoxin exhibits only weak modulation of the autonomic nervous system, whereas in ouabain this effect is very pronounced.

Given the aforementioned dose dependency of the steroid effects and the specific differences in mode of actions, it is not surprising that ouabain and digoxin may act as antagonists. In fact, cardiotonic steroids do not have identical, but often-antagonistic effects. In dogs, ouabain increases lactic acid utilization by the myocardium. Yet, digitoxin inhibits lactic acid utilization by the myocardium [49]. Ouabain stimulates myocardial protein synthesis [50]. Digitoxin inhibits myocardial protein synthesis [51]. Contrary to digitoxin, ouabain stimulates fatty acid utilization in the myocardium [52]. Ouabain has been used effectively to treat

digitalis intoxication in patients [reviewed in 13]. Corresponding reports are documented as early as 1902. Recent in vitro and in vivo studies confirm this well-known clinical observation [53]. Digitalis glycosides have long been used under the dogma that the aim of treating heart failure is to maximize the contractile force of the diseased myocardium. This led to a practice of using the highest tolerated dose of the inotropic glycosides. Dose was often increased until patients vomited or experienced disturbance of color vision. Under such circumstances the sympathomimetic effects of digitalis glycosides dominate. In ouabain the modulation of the autonomic nervous system prevails over weak inotropic effects. Oral administration of ouabain results in low but effective serum concentration that brings the vagomimetic effects to fruition [1]. This well explains why oral ouabain can be used to effectively treat digitalis intoxication in patients.

Different animal species have different sensitivities to cardiac glycosides. Rodents are particularly insensitive to cardiac glycosides. There are also major differences in pharmacokinetic properties. In humans ouabain is excreted rapidly mainly via the kidneys. In contrast, rats eliminate ouabain via biliary excretion [54,55]. About 90 percent of ouabain is excreted in the bile and 4 percent in the urine. In guinea pigs ouabain is completely excreted with the urine, while digitoxin is excreted by the liver via the bile [56]. Thus, in addition to differences in dose dependency and specific differences in mode of actions, species-specific characteristics have to be considered when results from experiments in animals are extrapolated to effects in humans. Due to differences in sensitivity and pharmacokinetics caution is advised when extrapolating experimental results in rodents to humans. Findings that ouabain in some experiments on long-term administration raises blood pressure in rats while digoxin lowers blood pressure [57] may have no predictive value for effects in humans.

6. THE PHYSIOLOGICAL STATE AND THE DOSE MAKE THE EFFECT

The autonomic nervous system regulates the cardiac function. The sympathetic and parasympathetic nervous systems are not “opposites”. Rather, a complex dynamic interaction occurs between them. Reciprocal control of cardiac vagal and sympathetic nervous activity, as seen during a baroreceptor reflex, as well as simultaneous co-activation of both autonomic limbs occur [58,59]. The effect of cardiac glycosides is dependent on the particular state of the autonomic nervous system. Thus, effects of cardiac glycosides are different depending on the physiological state of the experimental animal or patient. In patients with heart failure, vagal tone is reduced while sympathetic tone is high. Thus, in healthy volunteers other effects are observed as in cardiac patients. This also explains the well-known fact that patients have different, dose-dependent sensitivities to cardiac glycosides that need to be closely monitored in therapy. This is of special importance for the IV-administration of ouabain. Here the effects depend on the infusion rate. Abelmann confirmed this long known clinical experience: *“Thus, it is recommended that when digitalis glycosides are administered intravenously, this be done slowly, while monitoring systemic blood pressure, especially under circumstances where pressor effects are considered undesirable.”* [11]. On IV-administration of ouabain peak serum concentrations of >100 ng/mL [60] and 42–66 ng/mL [61] have been measured. That’s why in clinical practice concentrated solutions containing as standard 0.25 mg ouabain per 0.25 ml for iv-application preferably were diluted with 20 ml of 25% solution of dextrose. This procedure not only reduced the risk of intoxication due to high peak concentration as result of too rapid injection, but also reportedly improved the therapeutic effects due to the synergistic action of insulin. This has been textbook knowledge as early as the 1940s [62].

In heart failure a dysfunction of the autonomic nervous system is observed, characterized by excessive sympathetic drive accompanied by parasympathetic withdrawal. Beta-adrenergic blockade is used successfully to decrease hyperadrenergic drive. However, suppression of the sympathetic nervous system addresses only half of the autonomic imbalance. Ouabain with its pronounced vagomimetic and sympatholytic properties is well suited to fill this gap.

7. CONCLUSION

The search for circulating inhibitors of Na/K-ATPase in humans has led to new insights about possible pharmacological effects of ouabain. The pronounced dependence of the ouabain effects on the dose, the state of the autonomic nervous system and species-specific characteristics may explain many of the conflicting research results that have been published on experiments with ouabain. However, decades of clinical

experience with ouabain provide a yardstick by which all research results have to be measured. Observations at the bedside are more meaningful than speculative hypotheses based on experimental research. The mutually exclusive effects of ouabain and the inhibitor of the Na/K-ATPase observed in mammalian tissues do not support the hypothesis that this inhibitor is identical with ouabain, but favor the interpretation that De Wardener's "third factor" is something different, which also reacts to ouabain antibodies. Unlike the character in the novella by Stevenson, ouabain has no "split personality". There is no evil Mr. Hyde in ouabain.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
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