Cyclodextrins show promising results in cardiovascular disease through improvement of the lipid profile and regression of atherosclerosis

Introduction

Australian Institute of Health and Welfare (2021) reported 25% of all deaths in Australia was due to cardiovascular disease (CVD), with coronary heart disease being the main etiology. The aims of pharmacological treatment for CVD are reducing blood pressure and lipid levels with the goal of reducing mortality. The current blood pressure lowering agents recommended, based on evidence, are angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or thiazide-like diuretics (National Vascular Disease Prevention Alliance, 2012). Although these anti-hypertensive agents have shown to reduce major cardiovascular events such as myocardial infarction or stroke (Okin et al., 2004), there are some inconveniences in establishing the appropriate dose as some people may fail to respond to monotherapy (Milani, 2005; Cushman et al., 2002). The second arm of CVD management is lipidlowering therapy which consists of statins as first line therapy, followed by ezetimibe, bile acid binding resin and nictonic acid as second-line agents (National Vascular Disease Prevention Alliance, 2012). Statins have shown to reduce CVD mortality through its main effects on lowering LDL-C (Law et al., 2003).

Cyclodextrins, particularly 2-hydroxypropylβ-cyclodextrin (HPBCD), are cyclic structures which contain a lipophilic core which has been used to its advantage in therapeutic delivery of lipophilic pharmaceutical agents (Gould & Scott, 2005; Loftsson et al., 2005). Furthermore, HPBCD has been shown to increase cholesterol solubility thereby aiding in regression of atherosclerosis in-vitro (Liu et al., 2003; Atger et al., 1997) and in-vivo in murine models (Zimmer et al, 2016).

HPBCD has been extensively used in humans with Niemann Pick type C disease (NPC), which is a rare genetically inherited disease resulting in accumulation of cholesterol in tissues due to inability of intracellular transport, ultimately resulting in neurodegeneration. Studies have shown intrathecal and intravenous (IV) HPBCD to slow progress of disease in NPC patients (Ory et al., 2017; Hastings et al., 2019).

There have been many clinical studies using HPBCD in humans which have shown good tolerability with oral doses up to 24 grams and only diarrhea as a side effect at higher doses (Gould & Scott, 2005). Other routes such as intravenous and intrathecal has shown tolerability at greater doses of up to 2.5g/kg with no adverse events or toxicities (Matsuo et al., 2013).

This trial aims to study the effect of HPBCD on the atherosclerotic changes in a high-risk CVD patient based on its ability to solubilize cholesterol. HPBCD was administered intravenously for 33 days, separated into three phases based on dosage and frequency of HPBCD. Our results generated dramatic change in total cholesterol, LDL, and triglyceride along with liver function, in addition to decreased carotid plaque size.

Methods

CAVADEX trial

The recruited patient was a 58-year-old male with an extensive history of atherosclerotic disease requiring 5 stents in the past.

Throughout the entirety of the study, the patient was continued on his regular medication regime which consisted of antihypertensives, anti-cholesterol, and antiplatelets. In addition, no changes to diet or lifestyle were made during this trial to limit any confounding factors. The patient continued his regular lifestyle which consisted of 22 standard drinks per day and 20 cigarettes per day.

The purpose of this study was to investigate the effects of HPBCD on cardiovascular improvement through atherosclerotic changes. Several variables were studied to determine atherosclerotic change, which included: lipid profile, liver function test, urea and electrolytes, and carotid ultrasound. This trial was separated into three treatment phases with washout periods in between to study the trends in outcome measures, along with any influence in frequency or dosage of HPBCD. The first phase was treatment with 6g twice daily for a duration of 14days followed by a 7-day washout. The second phase consisted of 4g three times daily for 10 days, with subsequent washout for 12 days. The final phase was administering 6g three times daily for 9 days. CAVADEX® was the patented form of HPBCD used in the intravenous administration.

Results

The CAVADEX® trial was started with collecting baseline values with pre-treatment bloods which revealed markedly elevated cholesterol (10.6mmol/L) and triglyceride (20mmol/L), along with elevated ALT (56U/L) and GGT (101U/L). Following first week treatment of phase one with 6g twice a day, the blood parameters reflected decreasing values in cholesterol (9.3mmol/L) and triglyceride (13.7mmol/L). However, at this time, ALT (65U/L) and GGT (102U/L) showed no improvement. Thereafter on week 2, upon completion of phase 1, there was steady decline in cholesterol (6.4mmol/L) and triglyceride (8.1mmol/L). There was a decrease in GGT (83 U/L) noted for the first time following 2-weeks of treatment, while the ALT (67U/L) remained elevated. The second phase of treatment was commenced for 10 days, following a 7-day washout period. However, the bloods were collected just after the 7-day washout period which highlighted increasing cholesterol (6.9mmol/L) and triglyceride (13.6mmol/L), with no HPBCD treatment. One week following phase two commencement, improvement in all parameters were noted: ALT (48U/L), GGT (78U/L), cholesterol (5.5mmol/L), and triglycerides (8.9mmol/L). It is important to note, these values are at the lowest since the beginning of this trial. Upon completion of phase two- and 12-days washout, the blood reflects stable values of: ALT (46 U/L), GGT (82 U/L), cholesterol (5.4 mmol/L) and triglycerides (8.8 mmol/L). The final phase was successfully completed after 9 days of treatment with an increased dose, relative to the previous phases. Blood variables upon completion reflected all timelow levels of cholesterol (4.1 mmol/L), triglycerides (4.8mmol/L), ALT (37 U/L). In addition to the discussed variables, urate (0.506mmol/L to 0.249mmol/L) and LDL (3.7mmol/L to 1.5mmol/L) were shown to dramatically reduce after the completion of all three phases. Overall, a strong correlation between HPBCD treatment and improvement in lipid profile, and liver function has been established through this study, which is visualised in Figure 1. Moreover, the percent change amongst cholesterol, triglyceride and LDL was analysed amongst the three phases. Figure 2 suggests greatest percent change in cholesterol (39.62%) and triglycerides (59.50%) after phase I treatment while LDL (21.74%) responded greatly in phase II.

However, cumulative change amongst all three measures were drastic, showing 61.32% in cholesterol, 75.50% in triglyceride, 59.46% in LDL, as seen in Figure 2.

Another important consideration is the renal function which was stable throughout the entirety of the study (Table 1), suggesting nil renal impairment despite HPBCD's reliance on renal excretion.

Ultrasounds were conducted prior to the commencement of this trial to establish a baseline and following phase three to assess efficacy of HPBCD treatment. Imaging was used to assess the carotid arteries for atherosclerotic changes causing narrowing of the arteries. Results indicated a reduction in plaque size in the arteries, from 6.7x5.0x2.0mm to 6.1x4.7x1.7mm (Figure 3).

Hearing tests were also conducted prior to the trial and re-assessed following phase two of treatment. The baseline and post-treatment scans showed no changes in hearing.

Discussion

The results from this study reveal HPBCD acts on cholesterol and triglycerides molecules, most likely by solubilization in plasma with its lipophilic core and subsequently excreted in urine. The percent change in the lipid profile, particularly cholesterol and triglyceride were greatest in phase I, likely indicating 6g twice daily for 2 weeks was an effective dose in reducing atherosclerosis without posing toxicity. However, considering the cumulative percent change in lipid profile was substantial amongst all three variables, the duration of therapy is crucial for positive effects. Past studies have shown long term (up to 3years) HPBCD therapy proved no adverse events in humans (Berry-Kravis et al., 2018), thus considering long-term use for CVD is feasible. Urate also showed a great improvement upon 33 days of IV HPBCD treatment. Studies have shown a correlation between urate and risk of coronary heart disease (Wannametheee et al., 1997; Fang & Alderman, 2000), therefore this study suggests HPBCD possesses a multifactorial approach to reducing CVD.

Renal function was not compromised throughout the duration of this study despite increasing frequency and dosage of HPBCD. Gould & Scott (2005) extensively reviewed all literature with HPBCD use and determined it's safe and well tolerated amongst humans. However, there has been reports of nephrotoxicity in animal models with parenteral use of HPBCD (Perrin et al., 1978; Fromming & Szejtli, 1996; Frank et al., 1976), therefore witnessing normal renal function in this study was reassuring. There was a report on high frequency hearing loss with intrathecal HPBCD in one patient with Niemann-Pick disease (Maarup et al., 2015). However, this possibility was ruled out by studying hearing tests in this trial, which indicated no signs of ototoxicity. This trial has proven beneficial effects in CVD, however intravenous usage of HPBCD is not practical for long term therapy at home. New formulation has been designed to deliver HPBCD as a rectal enema (Rem Chol®). Through this means of application, greater bioavailability is attained as less drug is degraded compared to an oral preparation. Currently a trial is under investigation which involves CVD patients administering Rem Chol® for a month. Potentially, in the future, an oral preparation will be designed to ease the daily administration thereby reflecting in increased compliance.

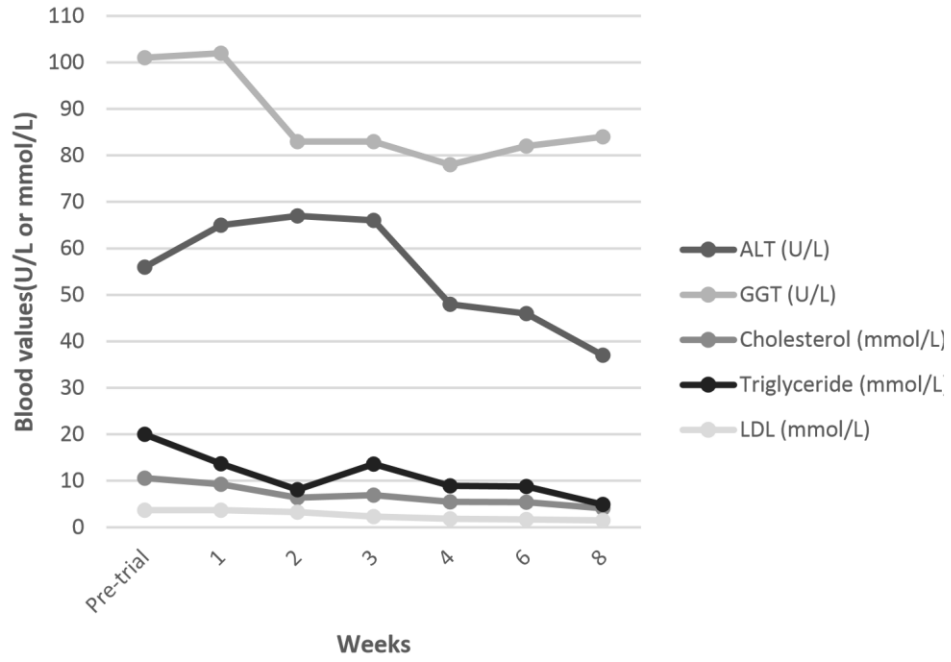

Figure 1. Graphical depiction of trends, over the eight weeks of HPBCD administration, in blood parameters involving ALT, GGT, Cholesterol, Triglyceride and LDL. Liver function and lipid profile parameters display a decreasing trend over the 8 weeks of HPBCD administration.

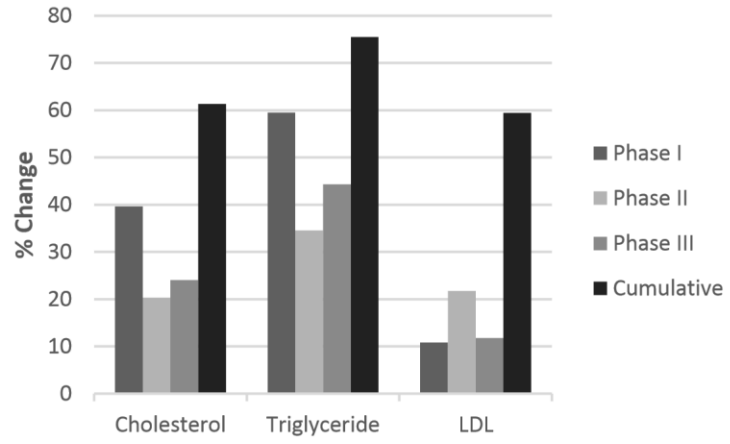

Figure 2. Analysis of lipid profile studying the percent change amongst cholesterol, triglyceride, and LDL in phase I, phase II, phase III and cumulative change. Cumulative change is distinct in all three parameters of lipid profile.

	Weeks					
	Pre-trial	**1**	**2**	**3**	**4**	**8**
Creatinine (µmol/L)	84	81	79	78	73	80
Urea (mmol/L)	5.4	4.7	5.3	4.7	4.1	4.4
Urate (mmol/L)	0.506	-	-	-	0.347	0.249
eGFR	88	>90	>90	>90	>90	>90

Table 1. Renal function measured through creatinine, urea, urate and eGFR is recorded over the duration of the study in weeks. Results indicate stable renal function over the 8 weeks of HPBCD administration, with a great decrease in urate observed.

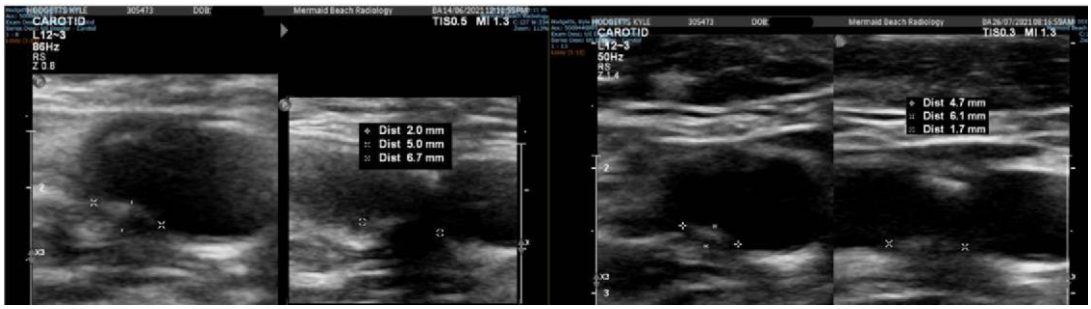

Figure 3. Carotid ultrasound performed pre -trial and after completion of phas e III which shows improvement of plaque size from (6.7x5.0x2.0mm) to (6.1x4.7x1.7mm).

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