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Review article

The potential use of transdermal drug delivery for the prophylaxis and management of stroke and coronary artery disease

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ABSTRACT

In 2013, cardiovascular disease was responsible for 30.8% (800,937) of all 2,596,993 deaths, or approximately 1 of every 3 deaths while stroke caused about 1 of every 20 deaths in the United States [1]. To put it in context, about 795,000 people continue to have a new or recurrent stroke (ischemic or hemorrhagic) [1] in the USA. Mechanical vascular recanalization and thrombolysis with tissue plasminogen activator are the only clinically useful approaches available now for the management of ischemic stroke [2]. Antiplatelet therapy with aspirin and/or clopidogrel is also a common practice utilized for the management of stroke, acute myocardial infarction and coronary artery disease [3]. There are two different but closely related approaches to improve therapy- to develop new disease-modifying agents or to find alternative drug administration routes for existing drugs. Transdermal drug delivery leverages the advantages of injections and tablets- painlessness, minimal invasiveness and the avoidance of presystemic metabolism and can potentially be applied to medications used for the prevention and/or management of coronary artery disease and stroke.

Contents

Introduction

In 2013, stroke was the fifth leading cause of death in the United States [4]. The disease caused approximately 1 out of every 20 deaths in the United States. It has been estimated that every 40 s, someone in the United States has a stroke, and someone dies of the disease approximately every 4 min [4]. Globally, stroke is the second leading cause of mortality resulting in approximately 6 million deaths every year and it is a major cause of long-term disability [5]. In the United States, the total direct and indirect cost for stroke was put at $ 65.5 billion in 2008 while in the European Union, the overall costs stood at € 27 billion [2].

Stroke takes place when blood flow to the brain is interrupted by an embolic or thrombotic occlusion of a cerebral artery (ischemic stroke) or by bleeding from a ruptured blood vessel (hemorrhagic stroke) [5]. Ischemic stroke commonly results from an occlusion of the middle cerebral artery (MCA) [6].

Bioenergetic failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, reactive

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oxygen species-mediated toxicity, generation of arachidonic acid products, cytokine-mediated cytotoxicity, activation of neuronal and glial cells, complement activation, disruption of the blood–brain barrier and infiltration of leukocytes usually accompany stroke [5]. Neurological deficits such as paralysis, dysphagia, aphasia, cognitive and behavioral changes are the major sequelae of stroke [7].

Effective pharmacotherapy for the management of stroke remains elusive. Currently, there is no medication capable of reversing the brain damage caused by this disease [8]. Prolonged rehabilitation, followed by life-long clinical support, is available for stroke survivors [8]. Even then, treatment modalities are extremely limited, partly because brain cells die when deprived of their blood supply rather quickly [9]. Over the last few decades, there have been significant improvements in stroke outcomes as a result of cardiovascular risk factor controls [4]. There are more positive interventions with regards to hypertension, diabetes mellitus, cholesterol and smoking cessation [4].

Currently, thrombolysis with tissue plasminogen activator and mechanical vascular recanalization are the only clinically accepted approaches available for the management of ischemic stroke [2]. Thrombolytics and neuroprotectants can be used to restore cerebral blood flow or to preserve the neurons affected by ischemic lesions respectively [6]. It is important to note that there is a narrow time window, coagulation abnormalities, intracranial haemorrhage and other contraindications. Consequently, only a small proportion of stroke patients can benefit from these two therapeutic modalities [2].

Atherothrombosis and inflammation play important roles in the pathogenesis of acute ischemic stroke [10]. Anti-platelet aggregation drugs, anticoagulants, neuroprotective drugs, and thrombolytics are used for the management of stroke patients but the efficacy of these medications is not satisfactory [11]. Aspirin is recommended for the management of ischemic stroke within 24 h of onset [10]. Statins have also been shown to be effective in the primary and secondary prevention of stroke [10].

Coronary artery disease (CAD), with its clinical sequelae of angina, myocardial infarction (MI), heart failure, and sudden death is the leading cause of death in advanced countries [12]. It is that in 2008, about 17.3 million people died from cardiovascular disease (30% of global deaths) and approximately 7.3 million of these deaths resulted from CAD [13]. Cardiac ischemia occurs when there is an imbalance between demand and supply of oxygen through the coronary arteries [14]. It has been postulated that the underlying cause of CAD is atherosclerosis [15]. Endothelial dysfunction, apoptosis and inflammation play critical roles in the initiation and progression of atherosclerosis [15].

Traditional risk factors implicated in CAD include tobacco smoking, obesity, dyslipidemias, diabetes and hypertension [16]. Several genes involved in lipid metabolism, inflammation and atherosclerosis have also been investigated [16]. Healthy lifestyle choices based on optimal nutrition, smoking cessation, and increased physical activity, as well as the use of therapeutic agents such as platelet and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors have reduced the incidence of CAD by almost 50% in high-risk populations [12].

Antiplatelet therapy with aspirin and/or clopidogrel is a common practice in the management of vaso-occlusive events such as stroke, acute myocardial infarction and coronary artery disease [3]. Aspirin irreversibly inactivates a key platelet enzyme cyclooxygenase (COX-1) thus inhibiting thromboxane generation while clopidogrel, a prodrug has no direct antiplatelet activity of its own, but its active metabolite binds to the platelet P_2Y_{12} receptor and irreversibly inhibits adenosine diphosphate (ADP)-induced platelet aggregation [3].

Transdermal drug delivery offers several advantages including sustained release, reduced dosing frequency and improved patient compliance [17]. This mode of drug administration also avoids some of the pitfalls of oral drug delivery such as presystemic metabolism and low bioavailability [18]. Inspite of the attractiveness of this method of drug delivery, there are inherent limitations. The stratum corneum, which is the outermost layer of the skin restricts the amount of drugs which can enter into the bloodstream [19]. There are numerous strategies which can be used to increase the transdermal diffusion of drugs and vaccines. These include prodrugs [20], iontophoresis, microneedles, sonophoresis and chemical penetration enhancers [21,22].

While several publications in the scientific literature have discussed the benefits of transdermal drug delivery, little has been documented regarding the potential advantages of this mode of administration for medications used in the management of stroke and coronary artery disease. This review seeks to fill this gap in knowledge and to discuss the research carried out in this field.

Percutaneous penetration of clopidogrel bisulfate

Clopidogrel (CPL), which is used for the prevention of atherothrombotic events acts by inhibiting adenosine diphosphate (ADP)-induced platelet aggregation [23]. The drug is a specific antagonist of the platelet P_2Y_{12} ADP receptor. CPL is a pro-drug from the thienopyridine group which is into an active thiol metabolite for it to exert its antithrombotic action [24]. The drug is subject to hepatic first pass metabolism and possesses a low oral bioavailability(50%) and a short elimination half-life (7–8 h) [25]. Recently, reports in the literature indicate that the transdermal delivery route may be beneficial for the delivery of CPL [25,26].

Sodium carboxymethylcellulose (SCMC), guar gum and tragacanth were used to formulate CPL-loaded transdermal therapeutic systems [25]. The authors observed that the formulation containing SCMC and tragacanth showed maximum release of 98.6% in 24 h, while transdermal patches formulated with SCMC and guar gum showed a minimum release of 42.9% in 24 h [25]. Darwhekar and colleagues also studied the influence of hydroxypropyl methylcellulose(HPMC), polyvinypyrrolidone (PVP) and ethylcellulose (EC) on the release of CPL [26]. It was stated that the combination of HPMC and PVP resulted in the release of 90.06% of the drug in 24 h while HPMC and EC caused 78.24% of the drug to be released in 24 h [26].

Interestingly, there are no published reports showing the influence of conventional enhancement strategies such as iontophoresis, sonophoresis, chemical penetration enhancers or microneedles on the transcutaneous flux of CPL.

Transdermal delivery of aspirin

Among the antiplatelet agents, acetylsalicylic acid is used extensively for the prevention and treatment of cardiovascular diseases (CVD) [27] including CAD and stroke. Aspirin acts by inhibiting platelet cyclooxygenase 1 (COX-1) and the synthesis of prostaglandin G2, the transformation of G2 into prostaglandin H2, the precursor of thromboxane A2 [27]. Acetylsalicylic acid (ASA) blocks thromboxane-dependent platelet activation by inhibiting cyclooxygenase [28]. In addition, acetylation of $serine_{530}$ in the platelet COX-1, results in the reduced generation of thromboxane A2 [29]. From a physicochemical standpoint, aspirin has a log P of 1.23 [30] which is well within the optimal range for transdermal diffusion [22,31]. The oral bioavailability of ASA tablets is about 40–50% and frequently, low dose ASA (75–325 mg daily) is used for the secondary prevention of cardiovascular and cerebrovascular events [32].