Research Article

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A Novel Device to Allow Blood-Brain Barrier Permeation by Molecules

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ABSTRACT

Here, we describe the investigation of a novel device for the molecular vaporization of liquid substances past the blood-brain barrier. This device vaporizes an active pharmacological substance using two energy sources simultaneously: high-frequency ultrasound and thermal induction. In this preliminary investigation, we tested this device on a 55-year-old healthy patient and quantified activity using metabolic imaging techniques. After intravenous injection, uptake in the brain reaches a maximum of 3.5% to 7.0% of the injected dose within 1 min of injection, and up to 15% of the activity in the brain is lost by 2 min after the injection. Of importance, in our study, semiquantitative calculation showed that the distribution of activity was 8.4% in the cerebral cortex and 91.6% in nasal sinuses. We therefore believe that administration of aerosol radiopharmaceuticals via nasal cannula could represent a valid alternative to intravenous administration of drugs for the targeting of medication past the blood-brain barrier.

KEYWORDS: Molecular vaporization; Blood-brain barrier; Exametazime; HER2-positive breast cancer

ABBREVIATIONS: HER2: Human Epidermal Growth Factor Receptor; HMPAO: Hexa Methyl Propyleneamine Oxime

INTRODUCTION

The blood-brain barrier consists of capillary endothelial cells, a basement membrane, glial podocytes, and a neurological membrane. It serves to limit the entry of substances into the brain parenchyma through the cerebral blood flow. It is a well-recognized protective system that prevents toxic substances and pathogens from damaging the brain. In particular, large and hydrophilic molecules are prevented from entering the brain by the blood-brain membrane; in general, only more-permeable hydrophobic molecules and small nonpolar molecules are able to diffuse across this barrier. Whereas the blood-brain barrier plays an important protective role, it also poses a significant challenge

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for delivering drugs to the brain. In fact, 100% of large-molecule neurotherapeutics and >98% of all small-molecule drugs are prevented from accessing the brain by the blood-brain barrier, which greatly limits the therapeutical potential of these agents [1]. Various strategies have been studied in the last 10 years to increase the permeability of the blood-brain barrier, such as the use of nanoparticle ligands [2]. The use of the central nervous system to overcome the blood-brain barrier has also been investigated [3]. The ability to deliver medications across the blood-brain barrier could have important therapeutic implications for many infectious, neoplastic, and neurologic diseases of the brain. In the present study, we investigate a novel medical device that can achieve molecular permeation of the blood-brain barrier.

MATERIALS AND METHODS

The device investigated in this study was designed by Bruno Brandimarte and built by Ginevri (Rome, Italy; www.ginevri.com) and DAV Electronics (Twickenham, England; www.davelectronics.com). The basic principle upon which the device operates is the integration of high-frequency ultrasound energy (3 MHz) and energy density (10/12 W/Cmq) with low amounts of thermic energy, which produces the desired molecular form without reaching heat-induced vaporization of the solution. These combined energies induce sublimation of the compound and produce micro drops of 0.2-0.3 microns in diameter. The effect is the production of a compound that is very similar to a gas without the production of re-condensate. Airflow delivered by a micro turbopump mixes with the gas, resulting in a positive pressure. This process is much faster than that involving common aerosols (in terms of seconds) and is electronically controlled by a microprocessor. The device is highly versatile and is able to interact with various platforms by the use of artificial intelligence. It was designed for medical use and can deliver medications at physiological temperatures through a gas media. Three different size models have been developed, with three reservoirs (5 cc, 10 cc, and 30 cc), for different experimental uses.

Operating Principle

The operation of the device is based on the formation of micro drops by means of high-frequency ultrasound (3 MHz). The fundamental difference between this and other, similar devices is that, in this device, the micro drops are not produced by the boiling of the solution due to heat transfer but rather by micro cavitation produced by mechanical vibration at ultrasonic frequency. Whereas boiling a solution to produce a vapor results in separation of the solvent from the solute, the use of vibratory cavitation to produce the micro drops allows unaltered vaporization of the solution. The diameter of the micro drops is determined by the geometric dimension of the vibratory turbulence, which is related to the wavelength of the ultrasound in the solution to be vaporized at a frequency of 3 MHz and 12 W/Cmq, the diameter of the micro drops produced is 200-300 nm. As the frequency of the ultrasound decreases, the diameter of the micro drops increases-for example, at a frequency of 1.8 MHz, the diameter of the micro drops is 300-400 nm. In addition, the size of the micro drops increases with the density of the solution (the denser the solution, the higher the required wavelength and, consequently, the larger the micro drops).

In vivo test

In this study, the device was tested on a 55-year-old healthy male volunteer with no history of pulmonary or upper airways diseases. All study-related investigations were performed in accordance with the guidelines of the Declaration of Helsinki and were approved by the Institutional Review Board at Azienda Ospedaliera dell'Universita' di Palermo (IRB#3/22). Exametazime (Ceretec) labeled with technetium metastable (99mTc) at a concentration of 4 mCi/mL (total activity, 20 mCi in 5 mL) was used. Radiolabeled exametazime was nebulized through the aerosol delivery system and administered via nasal cannula during a period of 5 min. Images were obtained by use of a double-headed gamma camera (Millenium GE), after the patient had inhaled the aerosol, by planar acquisitions in lateral-lateral projection (5 min, 256 * 256), anteroposterior acquisition (5 min, 256 * 256), and 360° tomographic acquisition (15 min, 64 views, 64 * 64). The acquisitions were made with the camera aimed at the head region. Regions of interest were placed at the level of the paranasal sinuses and brain, and the geometric meaning of the images was calculated.

RESULTS AND DISCUSSION

Images acquired after the patient had inhaled the aerosol show that 99mTc-labeled hexamethylpropyleneamine oxime (HMPAO) administered nasally reaches the brain. In fact, in both the planar images and the tomographic acquisitions, it was possible to observe cortex distribution. Regions of interest were placed over the brain region and the nasal region, and maximum and medium count rates were registered. From the semiquantitative calculation, it appears that the distribution of activity was 8.4% at the cerebral level and 91.6% at the level of the nasal sinuses.

The lateral-lateral acquisition Figure 1 shows deposition of the radiopharmaceutical in the nasal cavities and distribution in the brain. The anteroposterior acquisition shows homogeneous distribution of the radiopharmaceutical in the brain (Figure 2). Similar cortical uptake of 99mTc-labeled HMPAO is seen on transaxial reconstruction after tomographic acquisition of the head (Figure 3). On coronal (Figure 4A) and sagittal (Figure 4B) reconstructions after tomographic acquisition of the head, cortical uptake of 99mTc-labeled HMPAO is evident in the cortex but not in the lateral ventricles, which demonstrates the direct passage of the compound from the nasal cavities to the brain. The blood-brain barrier is a wide surface spanning 12-18 m2 in adults [4]; it regulates nutrients and ionic composition and protects the brain against pathogens and toxic compounds. In addition, this important barrier can prevent therapeutical agents from targeting the brain and limit their potential action.

Several approaches have been investigated to overcome this hurdle. One such approach is intrathecal administration of medication, which has limitations, including the invasiveness of the procedure. Serious complications, such as infection, bleeding, leakage, injury to nervous system structures, and fibrotic changes, are rare but can occur [5]. In addition, intrathecal administration may not achieve adequate drug concentration in the brain, thereby failing to achieve a therapeutical effect. Another approach to deliver medication past the blood-brain barrier is modification of the physicochemical properties of the drug. It has been established that, to improve blood-brain barrier permeability by passive diffusion, five key physiochemical parameters (molecular weight, ipophilicity, polar surface area, hydrogen bonding, and charge) must be optimized [6]. However, modifying the physicochemical properties of a drug is difficult and carries the risk of influencing the absorption, distribution, metabolism, and excretion properties of the compound, with questionable maintenance of the efficacy compound. The use of nanoparticle conjugates is a new method aimed at improving diffusion of the drug through the blood-brain barrier; limitations include low drug loading and high drug release

[7]. Other described methods include transient disruption of the barrier via chemical and physical methods, such as intracarotid injection of antineoplastic drugs with arabinose or mannitol [8], which is highly invasive and includes the risk of complications.

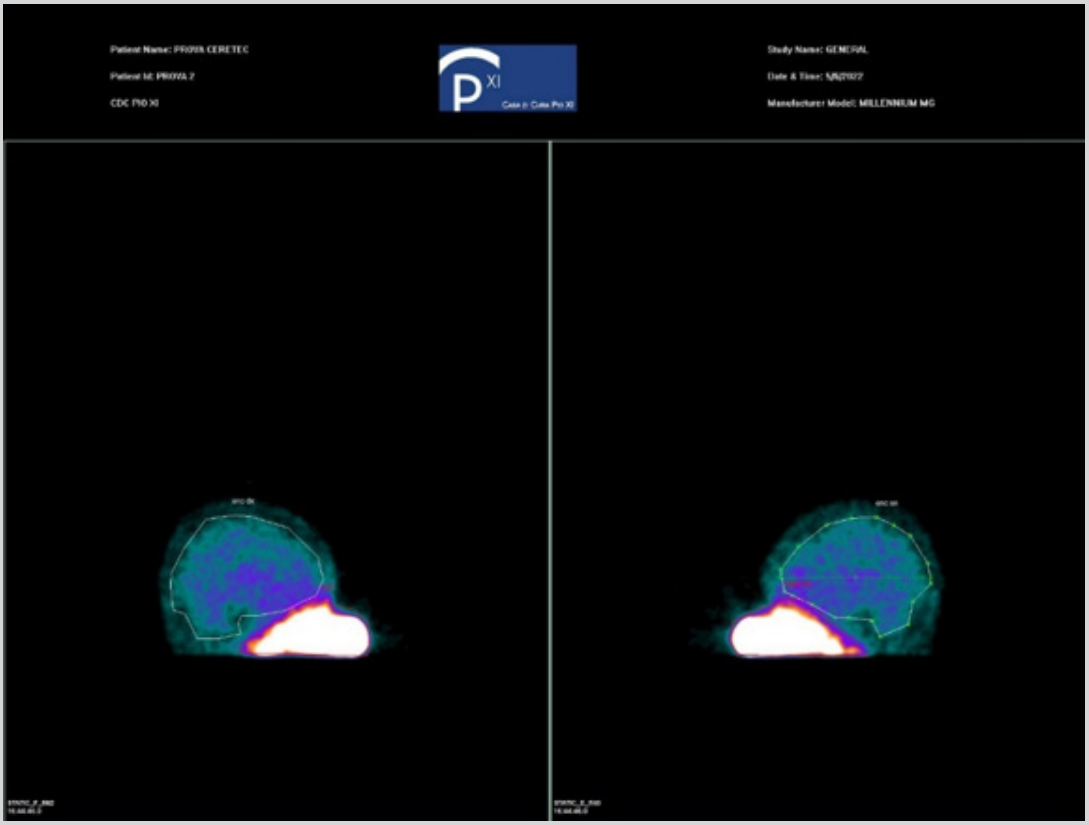

Figure 1: Lateral-lateral acquisition showing deposition of the radiopharmaceutical in the nasal cavities as well as its distribution in the brain. Regions of interest were placed over the brain region and nasal region, and maximum and medium count rates were registered.

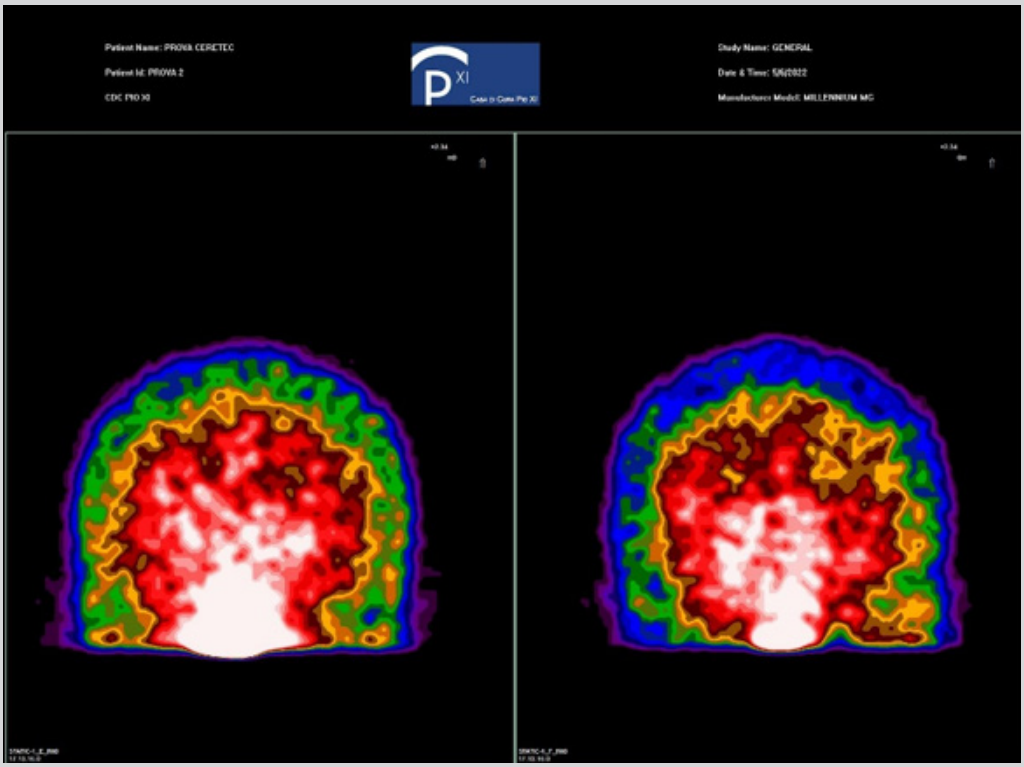

Figure 2: Anteroposterior acquisition showing distribution of the radiopharmaceutical in the brain.

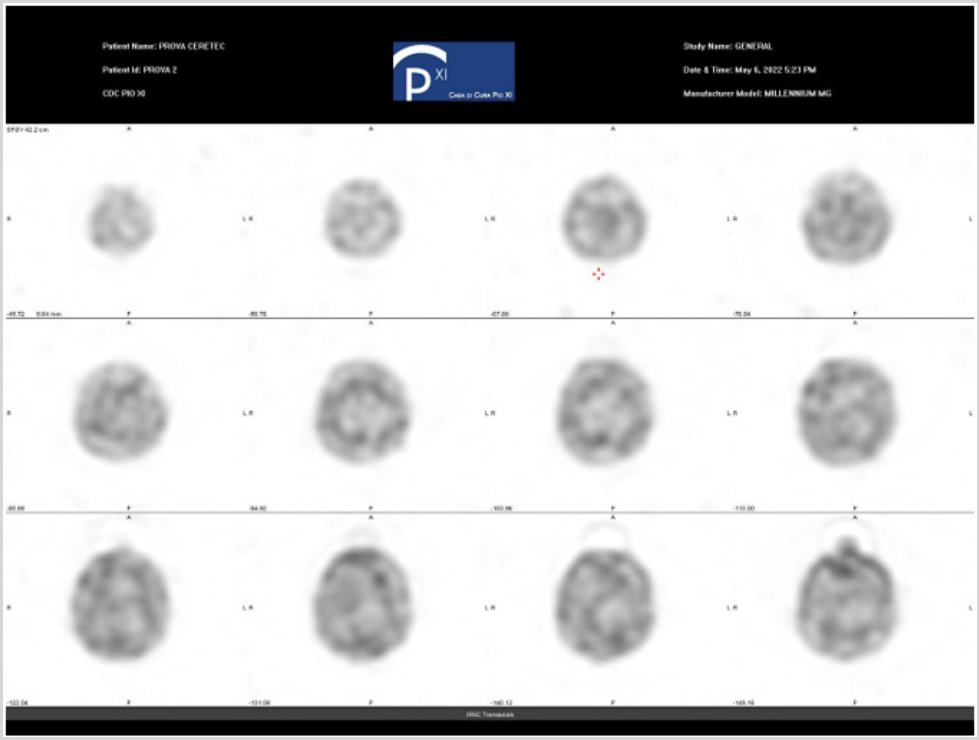

Figure 3: Transaxial reconstruction after tomographic acquisition of the head showing cortical uptake of 99mTc-labeled HMPAO.

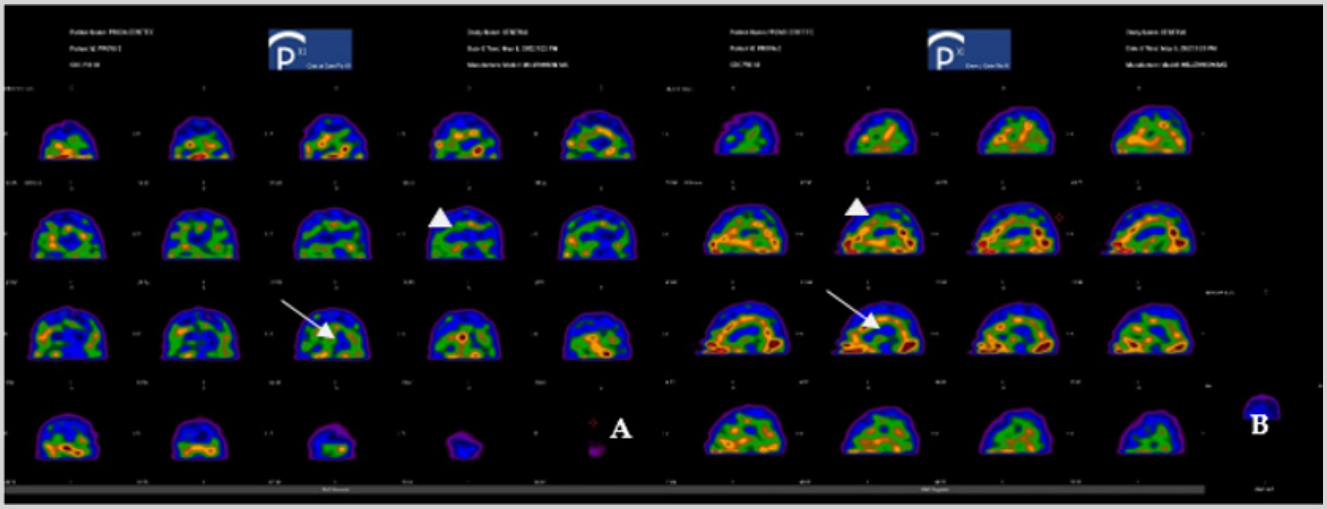

Figure 4: Coronal (A) and sagittal (B) reconstruction after tomographic acquisition of the head showing cortical uptake of 99mTc-labeled HMPAO. Arrows show lateral ventricles with no uptake of radiopharmaceutical; arrowheads show brain cortex with high uptake of 99mTC-labeled HMPAO.

Increasing the permeability of the blood-brain barrier could have important implications for the treatment of cancer for instance, for the management of human epidermal growth factor receptor 2 (HER2)–positive breast cancer. Highly effective HER2-targeted systemic therapies can control occult metastatic disease in all organs except the brain, which is of particular importance, as this type of cancer has a high risk of brain metastasis. In fact, brain metastasis has been observed as the first and only site of metastatic relapse in patients with advanced HER2-positive breast cancer and is associated with poor survival [9]. Improving the ability to deliver HER2-targeted therapies to the brain may reduce the risk of brain metastasis in this group of patients as well as in patients with small cell lung cancer, who also have a high risk of brain metastasis and for whom the available treatments have limited permeability in the brain. Prophylactic radiation has been advocated for these patients, although it can include substantial side effects [10].

Improving the permeability of neurologic medications may also increase the concentration of active medication in the brain. Attempts have been made to improve the targeting of pramipexole hydrochloride—a dopamine receptor agonist that is highly effective for the treatment of Parkinson disease although these relied on the use of complex, difficult to manage delivery systems [11]. As reported in the monograph for Ceretec [12], studies in healthy volunteers have shown that the 99mTc exametazime complex is rapidly cleared from the blood after intravenous injection. Uptake

in the brain reaches a maximum of 3.5% to 7.0% of the injected dose within 1 min of injection. Up to 15% of the activity washes out of the brain by 2 min after the injection, after which time there is minimal loss of activity for the next 24 h, except by physical decay of 99mTc. In our study, semiquantitative calculation showed that the distribution of activity was 8.4% in the cerebral cortex and 91.6 % in the nasal sinuses (7.7% of the total delivered dose reached the brain). Therefore, administration of aerosol radiopharmaceuticals via nasal cannula could represent a valid alternative to intravenous administration of drugs for the targeting of medication past the blood-brain barrier.

CONCLUSION

Our preliminary experience suggests that the use of this novel device could achieve blood-brain barrier permeation of molecules. Such an ability could potentiate the delivery of therapeutical concentrations of targeted neurologic or anticancer medications in a simple and easily applicable way, which could have substantial clinical and research implications. For example, several targeted medications for cancer cannot currently reach the brain, which may play a role in the high rates of brain metastases. Primary brain cancers could also likely benefit from better targeting with higher concentrations of chemotherapy drugs. Furthermore, improved permeability of the blood-brain barrier could allow medication to reach affected cellular systems in patients with degenerative brain diseases, such as Parkinson disease. Taken together, the advancements associated with this device have the potential to allow a broad spectrum of clinical trials.

ACKNOWLEDGMENT

The device described in this paper has the following patent: international patent #11910772.

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