The history of electrically assisted transdermal drug delivery (»iontophoresis«)

Axel Helmstädter

The first suggestions for the use of electricity for drug transport date from the mid-18th century. In a publication dated 1747, the Italian librarian Giovanni Francesco Pivati (1689 –1764) reported that the smell of Peruvian balsam hermetically sealed in a glass cylinder became apparent in the room after applying electrical current and could even be transmitted to another room by a wire. Other observations described by Pivati refer to an increased intensity of the smell of flowers by electrifying the vase and to the symptoms typical for mercury intoxication of a patient holding an electrified mercury containing glass cylinder in his hands. Those observations could, however, not be verified by independent investigators.

After Alessandro Volta found a simple method of producing a continuous flow of current (the Voltaic pile) in 1800, attempts to transmit chemical entities through membranes were made again. Important contributions were made by the French physician Bernard Raymond Fabré-Palaprat (1773–1833). He fixed a compress soaked with potassium iodide solution and one arm and connected it to the negative pole of a Voltaic pile. Another compress, soaked with starch solution, was fixed on the other arm and connected to the positive pole of the battery. A few minutes after the current flow had started, the colour of the starch solution turned blue. This was interpreted as proof for the electrically assisted transport of iodine through the body. Other researchers, however, were unable to repeat the experiment.

A further milestone in the history of iontophoresis was the "voltaic narcotism", a procedure for dental anaesthesia, introduced by Benjamin Ward Richardson ("father of dental iontophoresis", 1828–1896). From 1858 onwards, he used a mixture of 3 drachms of tincture of aconitine, 1 drachm of aconite extract and 3 drachms of chloroform which has been applied with the help of electric current.

In the 1870s, the German Hermann Munk (1839–1912) extensively investigated the current mediated transport of substances through porous membranes. He then thought about transmitting drugs through intact human skin as the skin is some kind of a porous membrane as well. To prove this theory, he tried to introduce strychnine hydrochloride into rabbits by means of electricity. After 20–25 minutes exposure to an electrified strychnine solution, spontaneous cramps were seen in the rabbits. He additionally claimed to have electrically introduced quinine sulphate and potassium iodide into his own body relying on the analytical detection of the alkaloid and the salt in his urine.

The strychnine experiments were repeated by the French physician Stéphane Leduc (1853–1939). His descriptions were published in several languages and became much more famous than those of Hermann Munk. He could show in a two-rabbit-experiment that strychnine sulphate is transported from the positive to the negative pole of the electric circuit. He also described the transdermal transport of potassium manganate.

Discussing the mechanisms of the transport of uncharged substances through intact skin, early authors claimed that liquid and substances were mechanically transported along with the flow of current ("just as a stream of water carries sediment with it"). This hypothesis was known as "cataphoresis" ("Kataphorese"), a term introduced by Hermann Munk in 1860 and predominantly used in the 19th century. Lateron, it became more and more evident that substances are also, indeed preferentially, transmitted as dissociated, charged ions. This phenomenon was intensively studied by Fritz Frankenhäuser (born 1868) who invented the term "Iontophorese" earlier than 1908. The most recently introduced term "electrically assisted transdermal drug delivery" does not refer to mechanistic considerations and should therefore be preferred.

Table 1: Iontophoretic treatment between 1858 and 1900

Scientist	Year of report	Drugs used
Richardson	1858	Chloroform/aconitine
Erb	1884	Various
Wagner	1886	Cocaine
Boccalari/ Manzieri	1888	Strychnine, atropine, quinine, KI
Lauret	1885	Various
Adamkiewicz	1886	Chloroform
Lambroso/ Matteini	1886	Chloroform
Corning	1886	Cocaine
Peterson	1888/1889	Cocaine
McGraw	1888	Cocaine
Cagney	1889	Potassium iodide
Edison	1890	Lithium salts
Imbert de la Touche	1891	Lithium salts
Gärtner/ Ehrmann <	1892	Mercury salts
Westlake	1892	Cocaine/carbolic acid, pyrazone
Morton <	1898	Cocaine

Table 2: Iontophoretic treatment at the end of the 1930's

Ions used	Indication
Zinc	Wound care, hay fever
Copper	Substitute for zinc
Silver	Pain relief
Chlorine/iodine	Softening of scar tissue

Mercury	Syphilitic ulcers
Magnesium	Warts
Lithium	"Gouty arthritis"
Cocaine	Anaesthesia
Adrenalin	Vasoconstriction
Quinine	Neuritis, neuralgia
Histamine	Rheumatic diseases

Table 3: Recent studies and applications of iontophoresis (since approx. 1950)

Scientist	Drug	Indication
Popkin et al.	Hyaluronidase	Scleroderma
Schwartz et al.	Hyaluronidase	Lymphoedema
Coyer	Citrate	Rheumatic arthritis
Stolman	Various	Hyperhidrosis
Rosenstein et al.	Various	Pain relief
Albrecht	Vincristine	Trigeminal neuralgia
Various	Peptides and Proteins	
Gibbons et al.	Non-invasive blood glucose measurement	

This study was generously supported by a grant the author received from The Bakken Research Foundation, Minneapolis, USA.

For details and references see Helmstädter, A.: The history of electrically-assisted transdermal drug delivery ("iontophoresis"). Pharmazie 56 (2001), 583–587.