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Historical perspectives

Endermatic, epidermatic, enepidermatic—The early history of penetration enhancers

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ABSTRACT

Already at the end of the 18th century, attempts were made to administer drugs transdermally. Several techniques were applied, including rubbing drug substances into the intact or wounded skin. Penetration enhancers were investigated as well, including human and animal body fluids, in particular gastric juice and saliva. In the 19th century, lipophilic solubilizers like chloroform and ether were tried. Although the experiments were mostly done against a pre-rational background some may be worth to be judged under scientific premises.

Contents

1. Introduction

Delivering drugs by other than oral routes has a long history and one might be amazed that intravenous application of drugs has a more than 350 year's tradition (Helmstädter, 2006) and thus, is much older than subcutaneous therapy which came up in the mid 19th century (Rosales, 1997). Lacking suitable syringes, intravenous application was more or less a surgical procedure and not routinely used for administering therapeutic agents circumventing the gastrointestinal tract. Its use was mainly experimental in exploring physiologic conditions like embolism or coagulation and few indications remained. Those included the removal of airway obstructions and diagnostics of apparent death by injecting a strong antiemetic – persons not actually dead started vomiting soon thereafter (Hager, 1831). Besides that, administration of drugs through intact or altered skin has been debated for centuries.

2. Early discussions about transdermal drug absorption

There have been many controversies whether substances could penetrate skin in general (Lehmann, 1996). An outstanding example is a treatise written by the German physician Heinrich Ludwig Westrumb (Westrumb, 1827). There, it is outlined that systemic effects can only be achieved when substances penetrate the skin and reach blood vessels to be distributed within the body. For example, it is described that opium exerts some activity when administered onto the skin including analgesia but also dizziness, drowsiness, sickness or feelings of insobriety. Strong laxatives like aloe or coloquintes exerted their obvious effects by merely being positioned on the abdomen. Westrumb even anticipated the well known transdermal administration of nicotine describing systemic effects of tobacco leaf pulp administered onto the stomach

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region including vomiting, dizziness and seizures. The ability of the skin to absorb substances from outside the body, originally called "Einsaugungskraft" could also been proven for inorganic substances, mainly mercury, which has long been used transdermally for syphilis therapy (Parascandola, 2009). Westrumb could show that mercury administered externally may soon be determined in body fluids like urine, blood or saliva. It has also been discussed, if and how far the human skin is able to absorb gases, water, aqueous solutions of minerals or non-aqueous solutions (Lehmann, 1996).

From the late 18th century onwards, several attempts were made to improve skin absorption by various methods which clearly represent somewhat like a pre-history of penetration enhancement. Those attempts became known under different terminology and comprise mechanical, physical, and chemical manipulations to reduce the barrier function of the skin. Simple rubbing, removing of the epidermis or the application of electrical current (iontophoresis, Helmstädter, 2001) have been tried as well as different agents promoting skin absorption of drugs. So the history of penetration enhancers spans at least two centuries, whereas "years of enlightenment" in this respect might actually have not begun before the mid 20th century. "Real progress" is said not to have been achieved before the advent of dimethyl sulfoxide in the early 1960s (Hadgraft and Lane, 2005).

3. Sophisticated terminology

At the beginning of his influential "Practical Treatise on materia medica and therapeutics", edited in several editions from 1876 onwards, the American physician Roberts Bartholow (1831–1904) discussed different application methods for drugs ("routes by which medicines are introduced into the organism") including those "through the external integument" (Bartholow, 1885). There, he distinguished "enepidermatic" application, where substances were diffusing as such or in solution through the skin without any mechanical aid. "Epidermatic" application includes mechanical manipulations like friction, while the term "endermatic" refers to methods which include the removal of the epidermis as primary absorption barrier, for example by blistering. This was usually done by applying concentrated ammonia solution or a plaster mass made of Spanish flies. A similar term, "endermic method" has already been used by the Prussian military physician Adolph Leopold Richter (1798–1876) who published an extensive work on his experiences in 1835 (Richter, 1835). In a usually painful process, he blistered the skin, removed the epidermis by scissors and spread powdered drug substances, mostly alkaloids like morphine directly onto the wound. Eventually, the terms "iatraliptice" or "iatroliptic" were in use as well. This term, which is said to have been introduced by the French physician Jean-André Chrestien (1758–1840) as "iatroliptice" in 1804/05 (Chrestien, 1804/5) and "iatraliptique" in 1811 (Chrestien, 1811) is derived from the Greek words "iatros" for physician and "aleipho" for greasing the skin with oil and basically means the skin absorption of substances from ointments and similar agents (Deslandes, 1839).

Besides this sophisticated terminology, the basic principles described here dominated transdermal drug delivery from the late 18th century up to the development of modern, matrix- or reservoir-type plasters, an application form which has its predecessors as well (Scheindlin, 2004).

Already in the late 18th century, the Italian physicians Francesco Chiarenti (1766–1828) and Valeriano Luigi Brera (1772–1840) had reported their extensive experiences with transdermal drug delivery, and became forerunners of the publications mentioned above. Brera called the method "Anatripsologia" which is also the title of his main publication which was printed in several editions (Brera, 1800). The term refers to the Greek verb "anatribein" for rubbing. So at first glance, Brera focuses on mechanical aspects, but also discusses the influence of agents on the penetration behaviour of drug substances.

4. Animal and human body fluids

The Italian physician describes several attempts to externally apply opium as a solution in gastric juice. This is based on the theory that opium could only penetrate deeply into the body if it has been digested to some degree (Brera, 1800, Fig. 1). Physiologists of the 18th century thought that a substance could only be sucked by the abdominal blood vessels (which was seen as an active process) in a digested state. Thus, it seemed totally reasonable to offer the blood vessels under the skin the material to be absorbed in a digested state as well. Chiarenti's first experiments were done with gastric juice form crows harvested according to the Italian scientist Lazzaro Spallanzani (1729–1799) who proved that digestion is not only a mechanical, but also a chemical process. Spallanzani is said to have firstly explored the role of gastric juice in digestion and did a lot of experiments in this respect (Müller, 1833). Brera did not only use opium externally in this way, but also other therapeutic agents with easily observable effects. Those included diuretic plants like Scilla maritima which was topically applied together with a little amount of gastric juice in an ointment. Similar results were seen with Digitalis and it is even described that a nurse showed severe diuretic effects after he had been applied the ointment carelessly to a patient without protecting his own hands.

As gastric juice was hardly available in large quantities, Brera started investigations using saliva as penetration enhancer, which he thought to have very similar properties. In fact, he also received

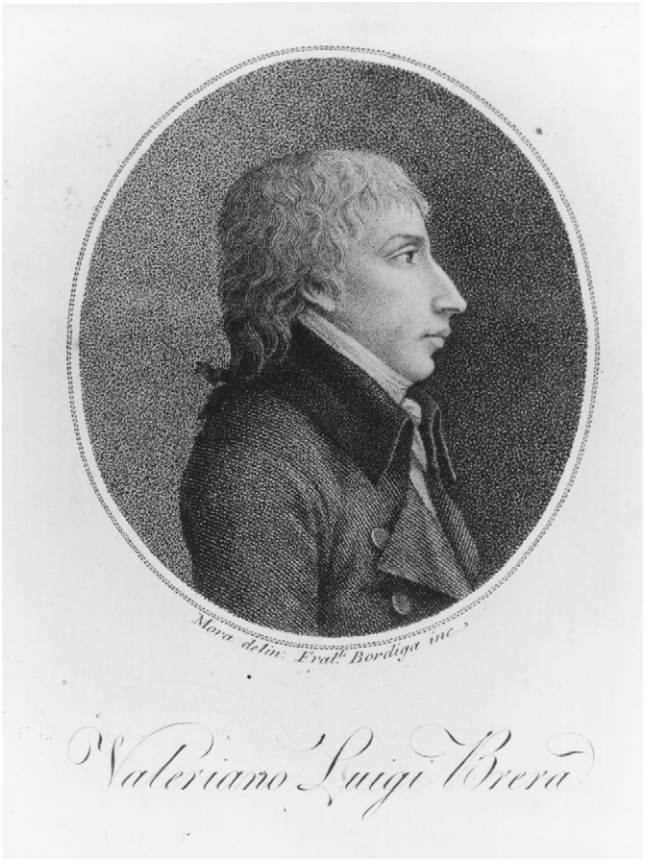

Fig. 1. Valeriano Luigi Brera (1772–1840) ©Biblioteca medica Statale, Rome, Italy, with permission.

obvious systemic effects with Opium, Scilla, Camphor and other agents applied externally. To be sure, he compared preparations containing gastric juice and saliva with others prepared without enhancer, with gum arabic, oil, meat extract, milk, and others and found agents of animal origin superior to those derived from the plant kingdom but still received the best results with gastric juice and saliva. Some effect was also seen with mechanical rubbing which is also recommended to additionally improve absorption from any kind of preparation. If gastric juice of non-human origin is used, it should be harvested from carnivorous animals while crows were regarded as such as they seem to be very keen on meat if having a choice. To receive considerable amounts, the birds should be forced to swallow a sponge containing perforated tube which is usually vomited soon thereafter. The German physician Immanuel Gottlieb Knebel also used crow fluid successfully but moved then to saliva by practical reasons. At the end he simply let the persons preparing or applying the ointments heavily spit into their hands (Knebel, 1804).

In his book, Brera is discussing almost every kind of body fluids regarding their properties as penetration enhancers including urine, serum, lymph, or even seminal fluid but usually found them only slightly effective. An exception is seen with bile which was considered similarly useful than gastric juice and saliva. So the Italian physician reported great success with an externally applied ointment composed of opium, calf bile and lard. Besides opium, Brera used Aconitum, Aloe, Arnica, Absinth, Puruvian balm, Camphor, Cinchona, Digitalis, Hyoscyamus, Guajak, Myrrha, Rhubarb, Scammonia or Scilla in a similar way.

5. Chloroform and ether

During the 19th century a variety of chemicals were detected or synthesized which also were tested for their ability to penetrate human skin or even act as penetration enhancers (Lehmann, 1996; Vogel, 1899). In this respect, chloroform, which has been synthesized in 1831 independently by Eugène Soubeiran (1797–1859) in France, Samuel Guthry (1782–1848) in the US and Justus von Liebig (1803–1873) in Germany, played a key role. In 1869, the British physiologist Augustus Volnay Waller (1816–1870) described his observations about a serious enhancement of transdermal delivery of alkaloids when dissolved in chloroform (Waller, 1869): "[. . .] We place various alkaloids dissolved in chloroform in contact with the skin, we quickly obtain evident symptoms of the absorption of theses agents, which may be carried to an extent sufficient to destroy life." Waller received most drastic effects, for example, by administering a 1:1 mixture of aconite tincture and chloroform. In an animal experiment, the foot of a rat was placed into an 1% chloroform solution of atropine. After 2–5 min, the animal's pupils began to widen significantly. With aqueous or alcoholic solutions, no or only weak effects were seen. Similar results were achieved with opium leading to somnolence or with strychnin leading to convulsions. Alcohol added to the chloroform solution further accelerated absorption. Using an endosmometer, Waller was also able to experimentally prove that "chloroform carries with it a certain amount of any alkaloid dissolved in it". Occasionally, penetration enhancing effects were also described for ether, so by Vogel who observed a stronger effect of externally applied chloral hydrate in combination with ether (Vogel, 1899). He also could show that salicylic acid penetrated the skin significantly when applied in an ether containing paraffin ointment. A respective preparation was thus recommended for the external treatment of rheumatism, massaging the ointment into the body should additionally exert a beneficial effect. Vogel also found that salicylic acid was much better absorbed than sodium salicylate and anticipated the fact that skin penetration works better with lipophilic agents, a fact which was clearly seen from the 1920s onwards (Rothman, 1929, 1943).

6. Conclusions

Attempts of Brera and others to enhance transdermal absorption by chemical matters did clearly not follow scientific principles of our times and were even based on baroque style considerations like "suction power". Additionally, not everything which was reported around 1800 can be taken for granted. However, it is well known that history is able to reveal relevant empirical knowledge although not always relying on a sound theoretical basis. In the case of penetration enhancers, at least the use of bile has some rationale, as it is well known that bile salts are possessing penetration enhancing properties, for example for steroids (Carelli et al., 1993) or even macromolecules (Sharma et al., 2006). Additionally it has long been recognized that lipophilic solubilizers like chloroform are able to promote percutaneous absorption (Rothman, 1943), but of course the use of chloroform is banned due to toxicological reasons. How far the use of crow's gastric juice and saliva may represent a rational principle of penetration enhancement may be further studied. In this context it seems interesting that with latherin, a compound with surfactant properties was found in horse saliva which might have penetration enhancing properties as well (McDonald et al., 2009).

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