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ERADICATION OF CHRONIC OSTEOMYELITIS RETROSPECTIVE ANALYSIS WITH PRACTICAL APPLICABILITY

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ABSTRACT

At the beginning of the 21st century it was established that all drugs have osmotic activity, the value of which increases with increasing their concentration in solutions. It was found that modern high-quality antibiotic solutions have different concentrations of antibiotics, so these solutions have different osmotic activity. It is shown that solutions of beta-lactam antibiotics as well as solutions of glucose at a concentration of less or more than 5% are hypotonic or hypertonic, respectively. Solutions containing a beta-lactam antibiotic at a concentration greater than 10% have been found to be hypertonic, which may cause local irritation. At the same time, solutions containing beta-lactam antibiotics in a concentration of more than 20% begin to have not only a local irritant effect, but also antiseptic, disinfectant and cauterizing effects. The reason for this is excessive hypertonic activity. The fact is that solutions of highly concentrated antibiotics have excessively high hypertonic activity, which provides them with an excessively strong dehydrating effect. In turn, excessive dehydrating activity can cause denaturing activity of antibiotics when applied locally, including injections. Therefore, solutions containing antibiotics in concentrations greater than 20% can be used as antiseptics and disinfectants similar to hypertonic sodium chloride solutions. In addition, solutions containing antibiotics in concentrations greater than 20% can lead to the development of inflammatory infiltrates, necroses and abscesses at injection sites, similar to 5-10% sodium chloride solutions.

Keywords: Antibiotics; antiseptics; disinfectants; inflammation; necrosis; abscess.

1. Introduction

It is known that injections of solutions of antibiotics, steroids, nonsteroidal anti-inflammatory drugs, vaccines and some other drugs sometimes cause local inflammation and abscess at the injection sites [1]. It is generally accepted that the cause of these complications is a violation of the injection technique and/or the rules of asepsis and antiseptics when injecting drugs [2]. Therefore, it is believed that local complications at the injection site arise due to the addition of infection [1-3]. However, the above ideas cannot explain all cases of local inflammation and abscesses at injection sites. The fact is that often intramuscular injections of drugs from different pharmacological groups almost instantly cause the appearance of such signs of local inflammation as local edema and local pain at the injection site [4,5]. Sometimes local pain occurs at injection sites of painkillers and local anesthetics [6].There are also reports that subcutaneous and intradermal injections of different vaccines can sometimes cause local inflammation of the skin and subcutaneous fat at the injection site immediately after the introduction of the vaccine [7,8]. In addition, there are reports of the urgent appearance of symptoms of local inflammation, including pain, not only with planned intramuscular injections and subcutaneous injections, but also with intravenous injections of many drugs, in cases when drugs enter the subcutaneous fat by mistake, inexperience or by chance [9-12]. It is noted that such local complications occur when injecting concentrated solutions of chemotherapy drugs, solutions of 10% calcium gluconate and solutions of 10% calcium chloride. Moreover, attention is drawn to the fact that concentrated solutions of chemotherapy drugs, calcium gluconate and calcium chloride have a pronounced anti-infective effect.

These reports indicate the possibility of immediate onset of local edema and local pain at the injection site of various drugs, including painkillers and local anesthetic drugs, as well as the possibility of abscess development at injection sites of anti-infective agents. The appearance of post-injection complications in these cases cannot be explained only by a violation of the injection technology and the rules of asepsis and antiseptics. In all likelihood, there may be another reason that we do not yet know and do not take into account.

2. Dependence of the local irritating activity of antibiotics on the value of their concentration in solution

For a long time, it was not assumed that one of the causes of such local complications as the rapid development of local pain and necrosis at the injection site could be the drugs themselves. However, at the beginning of the 21st century, it was reported that rapid local post-injection aseptic inflammation, necrosis and abscess can develop at the injection site of a solution of apomorphine hydrochloride, considered qualitative [13], as well as at injection sites of morphine hydrochloride, heroin and buprenorphine [14-17]. At the same time, the reason for the rapid development of these local post-injection complications was not known.

Almost at the same time, there were reports that all drugs have osmotic activity, the value of which increases with an increase in their concentration in solution [18,19]. In these reports, it was shown for the first time that solutions containing different concentrations of beta-lactam antibiotics have different osmotic activity. Based on this, it was suggested that in some cases beta-lactam antibiotics in the form of a "solution for injection" may be in high concentrations, which may give the antibiotic solution hypertonic activity. Therefore, such an antibiotic solution may cause nonspecific physico-chemical aggressiveness of the drug on the tissue at the injection sites [19]. To test this assumption, several series of experimental and clinical studies were conducted, in which the dynamics of the state of tissues at the sites of intramuscular and subcutaneous injections of beta-lactam antibiotic solutions of different concentrations and different osmotic activity were investigated. The first results showed that the dissolution of 1.0 g of dry powder of beta-lactam antibiotics in different solvents and/or in different volumes of the same solvent leads to solutions with different osmotic activity. At the same time, the value of osmotic activity of solutions turned out to be the higher, the greater the value of the total concentration of substances in the solution.

In particular, it turned out that solutions obtained by dissolving 1.0 g of dry cefoperazone sodium powder in 100 ml of water for injection, or in 100 ml of 0.5% glucose solution, are hypotonic. At the same time, solutions obtained by dissolving the same amount of antibiotic in 100 ml of 0.9% sodium chloride solution, or in 100 ml of 5% or 10% glucose solution, are hypertonuc. Similarly, the osmotic activity of the antibiotic solution changed with a change in its concentration in water for injection. In particular, an increase in the concentration of cefoperazone sodium from 1 to 10% increased the osmotic activity of the antibiotic solution from 36 to 495 mOsmol/l of water. At the same time, in clinical conditions, the condition of tissues was monitored at the sites of intramuscular injections of cefoperazone sodium solutions of different osmotic activity in adult patients. The studies were carried out using ultrasound and infrared thermography. The results showed that foci of hyperthermia, hyperemia, soreness, swelling and ultrasound hyperechogenicity appeared in 76% of cases at the sites of intramuscular injections of an antibiotic solution prepared by dissolving the powder in 0.9% sodium chloride solution, and in 6% of cases at the injection sites of an antibiotic prepared by dissolving it with water for injection. These data allowed the authors to show a higher local safety of hypotonic solutions of cefoperazone sodium during intramuscular injections compared with hypertonic solutions of this antibiotic. Therefore, to increase the safety of antimicrobials, it was first proposed to reduce their concentration in solutions before injection by dilution with water for injection [19,20].

In parallel the osmotic activity of solutions of other beta-lactam antibiotics was studied when their concentration changed and their effect on the

condition of tissues in live piglets during subcutaneous injections and applications into the conjunctiva of the eye. It turned out that an increase in the sodium content of sodium benzylpenicillin, sodium cefazoline or cefatoxim in solution from 1 to 10% increases the osmotic activity of the solution from 55, 53 and 60 to 570, 540 and 610 mosmol/l of water (respectively). At the same time, these antibiotics caused local inflammation of the skin and the organ of vision in piglets only when administered solutions containing these antibiotics at a concentration of 10%. Solutions containing these betalactam antibiotics in a lower concentration did not cause local inflammation [18].

In addition, the same study reported how the osmotic and local irritant activity of sodium chloride and glucose solution changes with changes in their concentration and subcutaneous injections. It has been shown that when the sodium chloride content of the solution is increased from 0.9 to 5.0%, its osmotic activity increases from 280 to 1470 mosmol/l water, and a 10% sodium chloride solution has an osmotic activity of about 3000 mosmol/l water. A similar but less pronounced osmotic activity was found in glucose. Solutions containing glucose at concentrations of 1, 5, 10, 20, and 40% were shown to have osmotic activity of 60, 300, 600, 1200, and 2400 mosmol/L water, respectively. At the same time, solutions of 1% glucose and solutions of 5% glucose caused very weak and short-term aseptic skin inflammation in piglets when injected subcutaneously. However, subcutaneous injections of 0.2 ml of 10 and 20% glucose solutions caused immediate development of strong and prolonged aseptic inflammation in the injection sites, but then after a few hours the inflammation symptoms gradually decreased and after 2 days were not noticeable. At the same time, subcutaneous injections of 0.2 ml of 40% glucose solution caused immediate and very strong aseptic local inflammation of the skin and subcutaneous fat at the injection sites, which did not disappear. Moreover, after 2 days, necroses were detected in all injection sites of the 40% glucose solution. At the same time, 0.9% sodium chloride solution did not cause skin inflammation in piglets when injected subcutaneously. However, subcutaneous injections of 0.2 ml of 5 and 10% sodium chloride solution caused immediate development of strong and prolonged aseptic inflammation in the injection sites. Moreover, in the case of injection of 5% sodium chloride solution, the inflammation lasted for several hours, but then gradually decreased and after 2 days was not noticeable. At the same time, subcutaneous injections of 0.2 ml of 10% sodium chloride solution caused immediate and very strong aseptic local inflammation of the skin and subcutaneous fat at the injection sites, which did not disappear. Moreover, after 2 days, necroses were detected in all injection sites of 10% sodium chloride solution [18].

Thus, betalactam antibiotics have osmotic activity commensurate with the osmotic activity of glucose. Therefore, solutions containing beta-lactam antibiotics in concentrations up to 5% are hypotonic. Solutions containing

betalactam antibiotics at a concentration of 5% are isotonic, and solutions containing betalactam antibiotics at a concentration of more than 5% are hypertonic. Solutions of 10% betalactam antibiotics, as well as solutions of betalactam antibiotics of lower concentration, but having similar hyperosmotic activity due to the additional content of sodium chloride or glucose, have a pronounced local irritating effect, causing local inflammation of the skin and subcutaneous fat when injected subcutaneously [18-20].

These reports confirmed the assumption that compliance with all standards of drug quality control, injection technology and rules of asepsis and antiseptics currently does not exclude the development of local inflammation at the injection sites of antibiotics. A study of the osmotic activity of solutions of betalactam antibiotics has shown that these sodium salts of these drugs have osmotic activity, which increases as the concentration of antibiotics in the solution increases and, with an increase in concentration of more than 5%, gives solutions hypertonic activity. Moreover, at a concentration of the antibiotic in a solution of 10% or more, the solution begins to have a local irritating effect. Then, a similar increase in the osmotic activity of solutions as the concentration of dissolved ingredients in them increased was shown with other anti-infectious drugs, in particular antiseptics [21-23].

Following this, it was reported that generally accepted standards for drug quality control do not include an assessment of the osmotic activity of injection solutions [24,25]. That is why not all injection solutions are isotonic. Moreover, it is precisely because of the lack of control over the magnitude of osmotic activity of solutions that some drugs, in particular antibiotics, may be hypertonic. Therefore, with intramuscular and/or subcutaneous injection, such hypertonic solutions can cause local inflammation at the injection site, which is manifested by local soreness, swelling, redness and hyperthermia [26]. Therefore, monitoring of local temperature using a thermal imager was proposed to assess local inflammation at the injection site of drugs [24,27,28].

3. Visual and infrared monitoring of the skin condition at the injection sites of antibiotics

Currently, new evidence has emerged that many antibiotics and drugs from other pharmacological groups have osmotic activity, and that the osmotic activity of drugs in the dosage form of "solution for injection" is still not evaluated, is not controlled during injections, and monitoring the condition of tissues at injection sites is not included in the standard for evaluating drug safety [29-33]. Therefore, there is still a possibility that subcutaneous, intramuscular and even intravenous injection of a drug that is considered high-quality today can cause local aseptic inflammation of a reversible, irreversible nature or even necrosis and post-injection abscess not because of a violation of the injection technology, but because of the hypertonic activity of the drug. The fact is that today no one knows the true strength of the dehydrating, local irritant and local inflammatory action of

any drug produced by a specific pharmaceutical company on a specific date, which is part of the production of a certain batch number and has certain quality indicators that inevitably change during the storage of the drug, depending not only on its duration, but also on the storage conditions of the drug.

Since the arsenal of antibiotics is expanding, and local complications at the injection sites of these drugs occur, as they did half a century ago [34,35], it is quite possible that some of these complications may occur due to the uncontrolled local irritating effect of antibiotics. Despite the fact that the local irritating effect of drugs is manifested by the immediate development of local aseptic inflammation, it can become irreversible and sometimes an infection can join it, which can cause a purulent abscess [36,37]. Therefore, monitoring the condition of the skin at the injection sites of antibiotics and other drugs remains relevant. And since local hyperthermia is an indisputable indicator of the onset of local inflammation, it follows that thermal imaging monitoring of local temperature dynamics can provide timely diagnosis of the presence of aseptic inflammation at the injection site. The correctness of this proposal is proved by the results obtained as a result of monitoring the skin temperature at the injection site of antibiotics with different osmotic activity.

In particular, it has been shown that local hyperthermia can be detected by infrared thermography after intramuscular administration of nonsteroidal anti-inflammatory drugs and some drugs from other pharmacological groups [19,24,25,33]. However, no one had previously used a thermal imager to monitor and evaluate the inflammatory effect of antibiotics and nonsteroidal anti-inflammatory drugs, despite reports of their local aggressive effect on tissues during injections up to the development of tissue necrosis, called Nicolau syndrome [38-44].

The above articles show that infrared monitoring of skin temperature at the injection sites of antibiotics allows timely detection of foci of local hyperthermia, which are symptoms of incipient local aseptic inflammation of an iatrogenic nature. In turn, an increase in skin temperature in the injection area can serve as an indicator of the local irritating or cauterizing effect of the administered antibiotic or other medication. In addition, the authors of the articles report that infrared monitoring of the dynamics of skin temperature at the injection sites provides documentation and archiving of the state of the injection site, which, in turn, provides a high-quality forensic examination of the causes of post-injection necrosis and abscesses [19,24,25,33].

4. Methods and drugs that prevent post-injection necrosis and abscesses

The discovery that antibiotics in high concentrations or in combination with other hyperosmotic drugs can have hypertonic activity, which can cause their local irritant, inflammatory and necrotic effects during subcutaneous and intramuscular injections, has allowed the development of several new ways and means of preventing post-injection

necrosis and abscesses. Initially, "Agent for topical injection chemoanesthesia" was developed (RU Patent No. 2274446). This drug represents an aquatic isoosmotic solution comprising 0.25% of novocaine, 1% of cefazolin sodium salt and 0.77% of sodium chloride. It has been shown that due to the isotonic activity, intramuscular injection of such a solution eliminates its dehydrating, local irritating and inflammatory effect on skeletal muscle tissue. In addition, this solution does not cause inflammation, necrosis and abscess of the skin and subcutaneous fat with accidental local interaction with them.effects during subcutaneous and intramuscular injections, has allowed the development of several new ways and means of preventing post-injection necrosis and abscesses.

Then the "Soft tissue injection method" was developed (RU Patent No. 2328318). The essence of this method is as follows. Initially skin area is chosen for anaesthesia. Then ultrasonic sensor is applied, and various skin areas are periodically pressed by finger, thus observing wavy changes of tissue structure under pressing on the screen. Place chosen for injection is that where deformation wave most precisely reaches chosen area. Further distance to chosen area from skin surface is measured with following tissue puncture with long injection needle on this depth with preliminary introduction of novocaine in amount 1-1.5 ml. Localization of medicinal infiltrate appearing in tissues is visualised, and if infiltrate created by novocaine injection is resolves within no more than 1.5 minutes, this area is intermittently introduced with medicinal agent dosed 1 ml under ultrasonic control of every introduction accuracy and infiltrate resolution intensity. Next portion of medicine is introduced after complete infiltrate resolution, created by last portion. In case infiltrate is intact within 3 minutes medical product introduction is stopped, and in medicinal infiltrate is introduced with 10 ml of novocaine solution.

After that, a "Method for chipping postinjection medicamental infiltrate" was developed (RU Patent No. 2333001). This invention can be used at the infiltrates caused by introduction of a hyperosmotic solution of a medical product in a tissue. For this purpose localisation and the size of an infiltrate are defined immediately, a needle is left in the place of injection. The method further includes defining an indicator of osmotic activity and volume of the solution ingected; detaching a needle from a syringe and injecting a water for injection cooled to 0°C into tissues with the second syringe in the volume providing normalisation of osmotic pressure of the solution injected with the subsequent applying of a bubble with ice for not less than 30 minutes. As first, half of the volume is injected in the form of consecutive injections on peripheries of the infiltrate formed, the other half of the volume being injected, through the needle left, into its central part. Method allows for preventing development of postinjection necrosis before an irreversible stage of inflammation thanks to depression of size of osmotic pressure of hyperosmotic agent injected.

5. Discussion

Intramuscular, subcutaneous and intravenous injections of solutions of antibiotics, nonsteroidal anti-inflammatory drugs and some other drugs can sometimes cause local inflammation, necrosis and abscesses at injection sites, despite careful compliance with medical technologies of injecting drugs [44-48]. For a long time there was no clear explanation of the cause of these local complications, until at the beginning of the 21st century, a previously unknown nonspecific local irritant effect of drugs associated with their hypertensive activity was discovered [18-21,24]. In particular, the relationship between the concentration of benzylpenicillin sodium salt and other betalactam antibodies in solutions with their osmotic activity, as well as with their local irritant and inflammatory effects was studied [18].

It turned out that an increase in the concentration of antibiotics in the solution from 1 to 5% turns their solutions from hypotonic to isotonic. Injections of such solutions do not cause aseptic inflammation and necrosis. An increase in the content of antibiotics in the solution of more than 5% and their combination with isotonic and /or hypertonic solutions of sodium chloride or glucose turns the solutions into hypertonic solutions. Injections of solutions containing antibiotics at a concentration of 20% or more cause severe aseptic local inflammation, followed by post-injection necrosis and abscesses at injection sites. In all likelihood, solutions containing antibiotics at a concentration of 20% and at a higher concentration have an excessively strong dehydrating effect, which causes a strong local irritant, antiseptic, disinfecting and necrotic effect when applied topically.

It follows from this that an increase in the concentration of antibiotics in solutions of more than 10% gives them a nonspecific hypertonic activity, which explains their local irritant, inflammatory, antiseptic, disinfecting and necrotic effect when applied locally. Therefore, solutions containing antibiotics in a concentration of more than 10% can be used for tissue disinfection. In turn, solutions of antibiotics intended for injection should have a concentration of less than 10% and should not have hypertonic activity.

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