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Nicolau Syndrome: Necrotic Activity of Drugs and Ways to Prevent Post-Injection Abscesses (In memory of Professor László A Gömze)

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Abstract

Post-injection abscess, which is the sad finale of Nicolau syndrome, continues to attract the attention of researchers due to the need to clarify the causes of this iatrogenic disease in order to develop effective measures for its prevention. For many years, researchers from all over the world have tried from different perspectives to explain the mechanism of the drugs effect that causes post-injection pain syndrome, infiltration, inflammation, erimatus skin damage, necrosis and abscess (Nicolau syndrome), but to no avail. This has been done only in recent years. There are findings in Russia that show that drugs considered to be of high quality today, in some cases, in addition to specific pharmacological activity, may have necrotic activity of a non-specific nature of action. The findings showed that according to the established pharmaceutical practice and in full compliance with the pharmacopoeia requirements for the quality of medicines, pharmaceutical products produced by different pharmaceutical companies, as well as those included in different series of the same pharmaceutical company, may have different compositions (formulations), contain different ingredients, therefore they may have different physico-chemical properties. In this regard, drugs of different serial numbers and/or different manufacturers, which are considered high-quality today, can be hypertonic solutions, have acidifying or alkalizing activity, have alcohols, aldehydes and heavy metal salts in denaturing concentrations. This is the reason that in some cases drugs have necrotic (cauterizing) activity. In this regard, to prevent Nicolau syndrome, it is proposed to reduce the physico-chemical aggressiveness of drugs. Today, this can be done successfully by diluting them with water for injection 2 to 8 times before injection.

Keywords: Nicolau syndrome, medicinal iatrogenism, inflammation, infiltration, necrosis, post-injection abscess, prevention, drugs quality

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Синдром Николау: некротическая активность лекарств и способы предотвращения постинъекционных абсцессов (в память о профессоре Ласло Гемзе)

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Аннотация

Постинъекционный абсцесс, являющийся печальным финалом синдрома Николау, продолжает привлекать внимание исследователей из-за необходимости выяснения причин развития этой ятрогенной болезни для разработки эффективных мер ее профилактики. Многие годы исследователи всего мира с разных сторон пытались объяснить механизм действия лекарств, вызывающих постинъекционный болевой синдром, инфильтрацию, воспаление, эритематозное повреждение кожи, некроз и абсцесс (Nicolau syndrome), но безуспешно. Это удалось сделать лишь в последние годы. В России удалось обнаружить, что лекарства, считающиеся сегодня качественными, в некоторых случаях помимо специфической фармакологической активности могут обладать некротической активностью неспецифического характера действия. Было показано, что по сложившейся фармацевтической практике и в полном соответствии с фармакопейными требованиями, предъявляемыми к качеству лекарств, лекарственные средства, произведенные разными фармацевтическими компаниями, а также входящие в состав разных серий одной фармкомпании, могут иметь разные составы (рецептуры), содержать разные ингредиенты, поэтому могут иметь разные физико-химические свойства. В связи с этим лекарства разных номеров серий и/или разных производителей, считающиеся сегодня качественными, могут являться гипертоническими растворами, обладать закисляющей или защелачивающей активностью, иметь в своем составе спирты, альдегиды и соли тяжелых металлов в денатурирующих концентрациях. Именно это является причиной того, что в некоторых случаях лекарства имеют некротическую (прижигающую) активность. В связи с этим для профилактики синдрома Николау предлагается уменьшать физико-химическую агрессивность лекарств. Сегодня это успешно можно сделать с помощью их разведения водой для инъекции в 2–8 раз перед инъекцией.

Ключевые слова: синдром Николау, лекарственная ятрогения, воспаление, инфильтрация, некроз, постинъекционный абсцесс, профилактика, качество лекарств

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INTRODUCTION

It is no secret that drug injections can cause general and local post-injection complications, among which necrosis and abscesses hold a specific place [1–3]. The cause of post-injection apostasis has not yet been precisely defined. In different years, it was assumed that the cause of these local post-injection complications is a violation of the rules of asepsis and antiseptics [4, 5]. However, it later became clear that local post-injection complications may be aseptic in nature [6–11]. In recent years, in Russia the findings show that when applied topically, all drugs can have a mechanism of action not previously described due to physico-chemical properties and/or factors of local interaction [12–17]. It is reported that the modern standard for drug quality control and standards for preclinical and clinical drug testing does not include accounting for their osmotic activity, and also

allows for different degrees of acidifying and alkalizing activity in medicines considered to be of high quality [18, 19]. Under these conditions, no one knows for sure the strength of the local dehydrating, acidifying or alkalizing effect of a particular drug. Therefore, today no one knows which medicine can cause a post-injection complication and why [18].

Damaging mechanism

Local post-injection inflammation, severe local pain syndrome, erythematous skin damage, necrosis and abscess remain the most striking, demonstrative and, at the same time, insufficiently explained [20–22]. This complex of local post-injection complications was first described about 100 years ago [23] and is called Nicolau syndrome [24–26]. There was initially a belief that these local complications arise due to violations of the rules of asepsis and antiseptics

and the subsequent addition of infection [27–30]. However, these concepts did not explain the cases of growing instantaneous local pain, local inflammation and local erythematous skin damage in areas of drug injection [30, 31]. In addition, the findings show that post-injection complications, including necrosis and abscesses, are often caused by antiseptics and antibiotics [1, 3, 27, 32].

At the same time, for many years, many researchers around the world have been looking to explain the pathological role of drugs, the injection of which caused Nicolau syndrome. The findings show that Nicolau syndrome can develop after injections of local anesthetics, steroid and nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, vaccines and some other drugs, as well as after injections of combined drugs [23, 33–36]. However, until recent years, no one has been able to explain exactly what the mechanism of action of drugs is, which is the cause of Nicolau syndrome progression. Today it is already clear that this was impossible, relying on the studied mechanism of action of drugs associated with their specific activity.

The situation changed dramatically after the mechanism of local action of drugs, not previously described, was discovered in Russia, associated with their nonspecific biological activity, which is given to drugs by their physico-chemical properties. It has been proved that it is the physico-chemical properties of drugs that can excessively change the state of body tissues during local interaction, give any drug necrotic activity and cause Nicolau syndrome [37].

These achievements in the field of physical-chemical materials science (or rather drugs science) were reported in October 2014 in Miskolc (Hungary) at the 3rd International Conference on Competitive Materials and Technology Processes (ic-cmt3), initiated and inspired by Professor Laszlo Gemse. At this conference, it was shown how the mechanism of local action of drugs changes when applied topically when the physical-chemical properties of drugs change [38, 39].

The study of the peculiarities of the local action of drugs, depending on their physico-chemical properties, showed that the solution of any drug can be hypotonic, isotonic or hypertensive, and can also be acidic, neutral or alkaline. Therefore, with local interaction (in particular, during injection), drugs do not have only a specific pharmacological effect, but also a non-specific physico-chemical effect that has not been described before [38–40]. In particular, the findings show that some drugs may have excessively apparent osmotic, acidifying or alkalizing activity, which, when injected with drugs, can cause their local irritating and cauterizing effects [18, 37–40]. The fact is that the modern standard of drug quality control does not include an assessment of their local post-injection effect (pain syndrome induction, inflammation, infiltration, erythematous skin damage, necrosis and abscess) [19]. This discovery made it possible to explain why drugs considered high-quality today can cause local inflammation, necrosis and abscess in areas of injection [38–41].

Prevention and control

The discovery of the mechanism of drug irritating and cauterizing action in areas of injection and the reasons why

modern medicines, considered to be of high quality, can have such an effect, explained not only the nature of Nicolau syndrome induction, but also indicated the right direction for the search and development of effective ways to prevent local post-injection complications. In particular, the discovery of the necrotic effect of drugs, manifested by local interaction in the presence of excessively high hypertensive activity, acid activity, or in the presence of alcohols, aldehydes and heavy metal salts in cauterizing concentrations [18, 38], explains the speed of the local pain syndrome induction [33, 42] and aseptic inflammation and necrosis that occur when injecting anti-infective agents [35, 36].

So, the lack of modern quality control of medicines allows for the use of injection solutions in medical practice, some of which have necrotic activity. Therefore, injections of such drugs can cause an urgent local irritant effect, which causes pain syndrome and aseptic inflammation. Prolonging the duration of local interaction for more than 5 minutes transforms the local irritant effect into a cauterizing effect and necrosis, which in a few days turns into an abscess.

Based on this, it is highly likely that drugs with a total concentration exceeding 10 % have necrotic activity, since all the ingredients dissolved in the drug solution have osmotic activity [18]. Therefore, solutions of medicines with a total concentration of 20 %, 40 % or more are hypertonic solutions and that is why injections of such drugs without prior dilution with water for injection can cause Nicolau syndrome induction as well as injection of a hypertonic 10 % sodium chloride solution.

In this regard, to prevent the Nicolau syndrome induction, there is no alternative to refusing injections of medicinal solutions that are hypertonic solutions just like a solution of 10 % sodium chloride. Such medicinal solutions can be determined by any doctor, since it is not necessary to measure their osmotic activity and it is enough to determine only the total concentration of all dissolved ingredients. If the total concentration of all ingredients is no more than 2 %, the absence of strong hypertensive activity and necrotic action during injection is highly likely. Therefore, such medicinal solutions can not be diluted with water for injection (unless they contain acids, alkalis, alcohols, aldehydes or heavy metal salts in cauterizing concentrations) before their injection. Conversely, if the drug solution has a total concentration of all ingredients exceeding 10 %, it is highly likely that there is a large hypertensive, dehydrating and necrotic activity. Therefore, before injection of such highly concentrated medicinal solutions, it is required to dilute them with water for injection by several times (2–8 times). It is clear that the multiplicity of dilution with water should be the more the greater the concentration of the solution.

In this regard, surgeons and oncologists should pay attention to the leading role of these physico-chemical properties of anesthetic, chemotherapeutic and other drugs from other pharmacological groups in local interaction during injections.

In the case of an erroneous injection of a drug solution that urgently caused post-injection inflammation with severe pain syndrome, any medical professional can use the

method invented in Russia for pricking a post-injection drug infiltrate [36]. The following is the formula of this invention:

“A method to prevent the induction of post-injection necrosis of tissues in areas of infiltration caused by the introduction of a hyperosmotic solution of a drug into the tissues, including determining the volume of the injected solution, leaving the needle in the injection area, disconnecting it from the syringe, injecting a second syringe into the tissues with a means inhibiting tissue damage, and applying an ice bubble for a period of at least 30 minutes, characterized in that the osmotic activity of the solution is preliminarily determined, the localization and size of the infiltrate are immediately determined, as a means of inhibiting tissue damage, water cooled to 0 °C is injected for injection in a volume that normalizes the osmotic pressure of the injected solution, and initially half of the volume is injected in the form of sequential injections along the periphery of the formed infiltrate, and the other half of the volume through the left needle into its central part”.

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