# Nonsteroidal anti-inflammatory drugs causing local inflammation of tissue at the site of injection

Sir,

Injections of drug solutions can be followed by the development of local complications such as phlebitis, cellulitis, phlegmon, and necrosis.[1,2] The development of these complications is not precluded by medical personnel's observing precisely the rules of aseptics and antisepsis as well as the instructions on applying drug solutions for injections.[3] In this case, development of inflammation can be caused by the local irritant action of a solution due to high concentration of active drug substance.[4,5] In a number of studies, it was found that irritant action on tissues can be characteristic of solutions not only with high (over 10%) but also with low indices of the concentration of active drug substance, for example, nonsteroidal anti-inflammatory drugs (NSAIDs).[6-8] We suggested that irritant action of the latter could be caused by the high total concentration of active drug substance and adjuvants which render the solution high osmolality. As local inflammation in warm-blooded mammals is accompanied by local hyperthermia, the study of changes in local skin temperature at the site of injections of NSAIDs solutions can assist in preclinical evaluation of their local safety *in vivo*. Hence, we aimed to investigate changes in pigs local skin temperature at the site of intramuscular (IM) injections of NSAIDs solutions with different osmolality.

The analysis of osmolality (mmol/kg) of NSAIDs solutions was carried out with the help of Vapor Pressure Osmometer Model 5600 (WESCOR-INC, USA). The following drugs were used: Ketorolac tromethamine 30 mg/ml solution for intravenous (IV)/IM use (Ketorol®, seriesA5054, Dr. Reddy's Laboratories Ltd., India) and metamizole sodium 500 mg/ml solution for IV/IM use (Analgin, series 521113, open joint-stock company "Dalkhimfarm" Russia). Drug solutions were diluted with sterile water for injections. The dynamics of skin temperature before and after the IM injections of 1 ml drug solutions at various dilutions were studied in healthy male Landrace pigs ($n$ = 10). They were fed on a balanced diet and had access to water *ad libitum*. Pigs were kept under standard conditions of temperature 25–26°C and good ventilation. The protocol for the experiment was approved by the Animal Experimentation Ethics Committee of Medical Academy. Before giving the injections, the pigs were placed on their backs, their limbs were fixed. After pretreatment of the pigs' skin with antiseptics, we injected room temperature solutions in the area of anterior abdominal wall at 4 cm intervals using 25G needles and 2.0 syringes. Thermometry and thermography of the sites of injections were performed with the help of infrared thermal imager ThermoTracer TH9100XX (NEC, USA) in the temperature range of 25–36°C within 60 min after the injections. The values of skin temperature over the surface of infiltrate produced by IM injection of 1 ml sodium chloride solution

**Table 1: The skin temperature of pigs at the injection site**

| Drug solutions | Temperature (°C) (mean±SD) | | | | |
|---|---|---|---|---|---|
| | Before injection | Immediately after injection | 5 min after injection | 30 min after injection | 60 min after injection |
| Sodiumchloride (9 mg/ml) | 35.5±0.8 | 28.8±0.8 | 35.3±0.9 | 35.8±0.8 | 35.2±0.9 |
| Ketorol® | 36.5±0.9 | 30.7±1.0 | 36.1±0.9 | 36.8±1.0 | 36.0±1.0 |
| Analgin | 36.1±0.8 | 29.0±0.9 | 36.4±0.8 | 37.6±0.9 | 36.9±0.9 |

9 mg/ml (series 160115, LLC "Zavod Medsintez", Russia) were used as control values. The obtained data were processed using the following programs: Thermography Explorer and Image Processor (NEC San-ei). Data were expressed as mean ± standard deviation and were statistically analyzed using Student's paired *t*-test to express the differences between groups. Comparison of the means was performed, and the differences were considered statistically significant when $P<0.05$.

Preliminary determination of osmolality of the studied solutions showed that the solutions were hyperosmotic in relation to normal osmolality index of blood plasma. Thus, Analgin osmolality index was 4520.0 mmol/kg, Ketorol® osmolality was 2971.0 mmol/kg. Analgin high osmolality was caused primarily by high concentration of active drug substance – metamizole sodium (500 mg/ml) in the solution but Ketorol® high osmolality was due to high total concentration of an adjuvant-propylene glycol (400 mg/ml). Osmolality of sodium chloride 9 mg/ml equaled 305 mmol/kg. During thermometry of the sites of injections, it was established that pretreatment of the skin with antiseptics and subsequent IM injection of any room temperature drug solutions initially reduced local skin temperature. The duration of local hypothermia was 4–5 min. Further observation revealed the appearance of local skin hyperthermia at the site of IM injections of ketorolac tromethamine 30 mg/ml (Ketorol®) and metamizole sodium 500 mg/ml (Analgin) solutions. Skin temperature at the site of injecting these solutions was 0.6–1.4°C higher compared with the initial values, the duration of hyperthermia was 60 min [Table 1].

The obtained data provide evidence that high osmolality of drug solutions result in local inflammation in infiltrated tissues causing the appearance of local skin hyperthermia over the area of infiltrate. Injections of the solutions diluted with sterile water for injections to osmolality index <1000 mmol/kg did not result in local skin hyperthermia.

Development of inflammation can be caused by the local irritant action of a drug on the infiltrated tissues. The supposition that irritant action of drug solutions can be caused by the high total concentration of active drug substances and adjuvants, which render the solution high osmolality, has been confirmed by the findings of our study. It was established that osmolality of ketorolac tromethamine 30 mg/ml solution was 9 times higher than normal osmolality of blood plasma. IM injections of NSAIDs solutions with high osmolality index were followed by the development of local skin hyperthermia at the site of injection. The obtained data confirm the results of previous investigations which provide evidence that local hyperthermia develops after injecting solutions of antibiotics and other drugs with high osmolality.[3,5,6] Reducing the osmolality prevents solutions by diluting them with sterile water for injections to osmolality <1000 mmol/kg allowed reducing the risk of the development of local inflammation.

To sum up, NSAIDs solutions have high osmolality index and can cause reversible local inflammation of tissues at the site of injection. Reducing the osmolality prevents solutions from being irritants. Monitoring the surface of the skin at the site of injection using infrared thermal imager allows assessing safety of drug solutions intended for injections *in vivo*.

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There are no conflicts of interest.

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## REFERENCES

1. Gyawali S, Rathore DS, Shankar PR, Kumar KV. Strategies and challenges for safe injection practice in developing countries. J Pharmacol Pharmacother 2013;4:8-12.

2. McGee AM, Davison PM. Skin necrosis following injection of non-steroidal anti-inflammatory drug. Br J Anaesth 2002;88:139-40.
3. Urakov A, Urakova N, Kasatkin A. Safe injections of antimicrobial drugs. J Infect Prev 2013;14 1 Suppl: S9.
4. Dadaci M, Altuntas Z, Ince B, Bilgen F, Tufekci O, Poyraz N. Nicolau syndrome after intramuscular injection of non-steroidal anti-inflammatory drugs (NSAID). Bosn J Basic Med Sci 2015;15:57-60.
5. Urakov A, Urakova N, Kasatkin A, Chernova L. Physical-chemical aggressiveness of solutions of medicines as a factor in the rheology of the blood inside veins and catheters. J Chem Chem Eng 2014;8:61-5.
6. Kasatkin AA. Effect of drugs temperature on infrared spectrum of human tissue. Thermology Int 2013;23:72.
7. Mishra A, Veerasamy R, Jain PK, Dixit VK, Agrawal RK. Synthesis, characterization and pharmacological evaluation of amide prodrugs of ketorolac. Eur J Med Chem 2008;43:2464-72.
8. Urakov A, Urakova N, Kasatkin A, Reshetnikov A. Infrared thermography skin at the injection site as a way of timely detection injection disease. Thermology Int 2015;25:30.



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