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**Experimental study of caffeine influence on antiexudative activity of known NSAIDs of different chemical structure**

**Abstract:** Antiexudative activity of combinations of some anti-inflammatory drugs with caffeine is shown in the experiment. It is found that caffeine potentiates antiexudative activity of diclofenac sodium, ibuprofen and paracetamol. It is discovered that the composition of caffeine with ibuprofen has more intensive antiexudative effect than the composition of caffeine with diclofenac sodium and paracetamol.

**Keywords:** ibuprofen, diclofenac sodium, paracetamol, caffeine, antiexudative activity.

The problem of pharmacological regulation of inflammation is very important for the modern medicine. Inflammation acts as a major pathogenetic component of various diseases, therefore correction of inflammation processes is considered as one of the major problems of pharmacology[[1]](#footnote-1). There is a significant number of drugs used for inflammation treatment[[2]](#footnote-2),[[3]](#footnote-3). These drugs possess many useful properties, in particular, they have anti-inflammatory, analgesic, and antipyretic activities[[4]](#footnote-4),[[5]](#footnote-5),[[6]](#footnote-6). It is well known that the combination of several components in a single medicinal product promotes its specific action spectrum[[7]](#footnote-7). It is also known that caffeine is able to enhance analgesic, anti-inflammatory and other effects of drugs[[8]](#footnote-8),[[9]](#footnote-9),[[10]](#footnote-10). Therefore, it was promising to study in experiments using laboratory animals the effect of caffeine on antiexudative activity of known drugs of different chemical structure: ibuprofen (a derivative of propionic acid), sodium diclofenac (a derivative of phenylacetic acid) and paracetamol (an aminophenol derivative).

**Materials and methods.** Exudative inflammation serves as a classic example of an acute one[[11]](#footnote-11). Experimental researches have been conducted in order to study antiexudative activity of combinations of the investigated compounds with caffeine. Reserches were aimed at comparative evaluation of diclofenac sodium, ibuprofen, paracetamol and their compositions with caffeine. All the experiments were performed in accordance with the modern recommendations[[12]](#footnote-12). Antiexudative action of examined compounds and combinations was studied on white male rats of the WAG strain weighing 180-220 g using a formalin edema experimental model. Animals were divided into 8 groups, 6 animals in each group. Animals of the 1st group serve as a control, 3% starch mucilage was once orally intragastrically administered to animals of this group. Diclofenac sodium (8 mg per 1 kg of body weight of the animal[[13]](#footnote-13)) in the form of 3% starch mucilage suspension was once orally intragastrically administered to the animals of the 2nd group. Ibuprofen (6 mg per 1 kg of body weight of the animal) was administered to the animals of the 3rd group under the same conditions. Paracetamol (30 mg per 1 kg of body weight of the animal) was administered to the animals of the 4th group under the same conditions. Caffeine (0.6 mg per 1 kg of body weight of the animal) in the form of 3% starch mucilage suspension was once orally intragastrically administered to the animals of the 5th group[[14]](#footnote-14). Conversion of the human doses for rats was done by using the ratio of species sensitivity[[15]](#footnote-15). Combinations of examined drugs with caffeine in the form of 3% starch mucilage suspension were once orally intragastrically administered to the animals of the 6th, 7th and 8th groups, i.e. diclofenac sodium, ibuprofen and paracetamol were administered in the indicated doses and concentrations, but with the addition of caffeine to each drug in the form of 3% starch mucilage suspension at the rate of 0.6 mg per 1 kg of body weight of the animal (the groups 6th - 8th correspondingly)[[16]](#footnote-16). Examined nonsteroidal anti-inflammatory drugs (NSAIDs), their combinations with caffeine, and starch mucilage (control group) were administered 3 hours after creating of experimental edema and 1 hour before the maximal experimental edema development. Exudative inflammation was modeled by subplantar injection of 0.1 ml of 2% formalin solution in the rat hind paw. Paw volume was measured using oncometer[[17]](#footnote-17) before the experimental formalin injection and 1hour after drugs administration at the moment of maximal swelling.

Laboratory animals employed in the study were kept in experimental biological clinic of KhNMU following the norms of the storage, care and feeding approved by the principles of "European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes" (Strasbourg, 1986)[[18]](#footnote-18) and the decision of the Third national Congress on Bioethics ( Kyiv, 2007)[[19]](#footnote-19). Statistical calculations were performed by conventional methods[[20]](#footnote-20).

**Results and discussion.** Results of investigation of antiexudative activity of drugs and their combinations with caffeine are shown in Fig. 1.

0

10

20

30

40

50

60

70

80

90

100

2

3

4

5

6

7

8

Antiexudative activity, %

Groups

Fig. 1. Investigation of caffeine influence on antiexudative activity of NSAIDs of different chemical structure in experiments on rats.

2 – diclofenac sodium; 3 – ibuprofen; 4 – paracetamol; 5 – caffeine; 6 – diclofenac sodium + caffeine; 7 – ibuprofen + caffeine; 8 – paracetamol + caffeine

Experimental study of antiexudative activity of compounds of different chemical structure and their compositions with caffeine has showed that all investigated NSAIDs, adjuvant caffeine and its compositions with NSAIDs significantly reduced the swelling as compared with the control.

Introduction of pure diclofenac sodium inhibits edema by 33%. The composition of diclofenac sodium with caffeine significantly reduces formalin edema as compared with the control by 47% (P <0.01). This fact allows concluding that caffeine is able to enhance the antiexudative activity of diclofenac sodium.

The composition of ibuprofen with caffeine appears to be the most effective. This composition significantly inhibits development of formalin edema (P <0.001). This fact is proved by indicators of paw size which are almost identical with the original size (inhibition by 95%), while pure ibuprofen reduces the swelling by 37% (the difference between activity of pure ibuprofen and its combination with caffeine is statistically significant – p <0.001).

Administration of pure paracetamol inhibits edema by 19%, administration of pure caffeine inhibits edema by 35%. The composition paracetamol + caffeine appears to be more effective – it reduces edema by 74%, i.e. paracetamol and caffeine in a definite way mutually potentiate antiexudative activity.

**Conclusions.** All compositions of examined compounds of different chemical structure with caffeine show more pronounced antiexudative activity than pure substances, therefore caffeine potentiates antiexudative activity of diclofenac sodium, ibuprofen and paracetamol. Composition of caffeine with the propionic acid derivative (ibuprofen) possesses more intensive antiexudative action than the composition of caffeine with phenylacetic acid derivative (diclofenac sodium) and aminophenol derivative (paracetamol).

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