

THE APPLICATION OF INTRAVENOUS PARASETOMOL IN COMPLEX THERAPY OF PAIN AND HYPERTERMIC SYNDROM IN PATIENTS WITH POLYTRAUMA AND IN PATIENTS OF NEUROREANIMATION GROUP

Cherny V.I., Kolesnikov A.N., Stasiuk V.N., Dergunov D.V., Chernutsky S.O.

Donetsk National Medical University named after M.Gorkyi

Summary. In this paper the authors present the results of independent studies of the efficacy of the intravenous form of paracetamol in patients of neuroreanimation group with severe hyperthermic syndrome and in patients with polytrauma for correction of pain syndrome.

It was shown, that paracetamol is more effective than acetylsalicylic acid in complex therapy of hyperthermic syndrome. Good results of application of paracetamol in a combination with narcotic analgesic are received at complex correction of a pain syndrome.

Key words: *paracetamol, hyperthermic syndrome, pain syndrome.*

The major objective of intensive care in neurocritical patients (severe traumatic brain injury, severe stroke, meningoencephalitis) is to maintain an optimal flow of oxygen-rich blood to the brain. Therefore, prevention and treatment of recurrent episodes of cerebral ischemia, such as secondary ischemic attacks caused by systemic and intracranial pathological processes, are of crucial significance. Systemic processes include hypotension, hypoxia, hyper- and hypocapnia, electrolyte disorders, anaemia, pyrexia, hyper- and hypoglycaemia, and the acid-base balance disturbances. Intracranial factors of secondary ischaemia include intracranial hypertension, cerebral oedema, hydrocephalus, intracranial infectious complications, seizures, etc. One of the major systemic pathological processes in this range is hyperthermia.

Hyperthermic syndrome in neurointensive patients may be caused by several factors. The development of hyperthermia due to infectious complications (aspiration syndrome, pneumonia, bedsores, phlebitis, etc.) should not be disregarded. However, the greatest risk for these patients is the so-called "central hyperthermia" as a result of hypothalamus stimulation (diencephalic syndrome). This hyperthermia requires urgent measures, because it leads to a significant increase in oxygen consumption and aggravates secondary hypoxic damage of the CNS.

An increase in the body temperature up to hyperpyretic values is characterized by changes in the functions of internal organs and their systems. Disorders of CVS function are exacerbated, and the so-called hyperthermal cardiovascular syndrome is developed, presenting with the following symptoms:

- aggravated tachycardia;
- decreased stroke volume;
- cardiac output is provided mainly due to increased heart rate;
- microcirculatory disorders;
- signs of SLUDGE syndrome, disseminated intravascular coagulation of blood proteins (DIC syndrome) and fibrinolysis; and
- acidosis. The increased acidosis is accompanied by:
 - elevated both ventilation and release of carbon dioxide;
 - increased oxygen consumption; and
- decreased oxygen-haemoglobin dissociation. The latter combined with circulatory disorders aggravates hypoxemia and hypoxia. This, in turn, causes the activation of glycolysis, and aggravations in disturbed energy supply of tissues and the degree of acidosis.

Modern trends in postoperative analgesia are characterized by the following: There has been a trend in significant limitations of the conventional use of opioid analgesics, not only because of increased requirements to strict accounting of narcotic analgesics, but also due to their low efficacy and the occurrence of adverse effects (especially in elderly and senile people), manifested in respiratory depression, hypodynamia, nausea, vomiting, urinary retention, pruritus, drug dependence and the potential for addiction;

There is a wider use of modern most effective non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and intravenous paracetamol. The frequency of their use varies from 45 to 99%;

A trend has been developed in the application of multimodal postoperative analgesia with the simultaneous administration of several anesthetics and adjuvant agents exerting their effects on various mechanisms of pain syndrome development and preventing adverse events caused by analgesics. There are ongoing studies on the well-balanced selection of optimal combinations of analgesics and adjuvant agents aimed at reducing the toxicity of drugs.

Paracetamol has analgesic and antipyretic effects. It inhibits cyclooxygenase I and II in the CNS, and affects pain centers and thermoregulation. It does not affect the synthesis of prostaglandin (PG) in the peripheral tissues, therefore, has no negative impact on the water-salt metabolism (sodium and water retention) and gastrointestinal mucosa.

The maximum concentration (C_{max}) is observed in 15 min, and amounts to 15-30 µg/mL. The volume of distribution is 1 L/kg. The drug poorly binds to plasma proteins. The drug penetrates the blood-brain barrier (BBB). The drug is metabolized in the liver, with the subsequent formation of glucuronides and sulfates. A minor portion (4%) is metabolized by cytochrome P450 to form an intermediate metabolite (N-acetyl-p-benzoquinoneimine). Under normal conditions, it is rapidly neutralized by reduced glutathione, and excreted in the urine after binding to cysteine and mercaptopurine acid.

After the intravenous dosage form became available, the drug's value was significantly increased and indications for the use were broadened. The intravenous dosage form is far superior to tableted dosage forms in terms of safety, because of the possibility to better manage the drug plasma concentrations. This advantage is supported by practical clinical trials which have found significant variations in the plasma concentrations of paracetamol up to dangerously high levels after oral use compared to the intravenous administration.

Paracetamol depresses the "central" pathway of synthesis of prostaglandins that regulate the process of body temperature increase. The drug is prescribed in a single dose of 10-15 mg/kg.

The aim of the study was to assess the efficacy of the intravenous dosage form of paracetamol in achieving an antipyretic effect in patients with central hyperthermia being treated at the anaesthesiology and intensive therapy unit (patients with traumatic brain injury, stroke), and an analgesic action in patients with multiple trauma.

MATERIALS AND METHODS

The study was conducted in the setting of the Anaesthesiology and Intensive Care Unit and the Department of Neurology at the Clinical Miners Hospital. The ICU contains 6 beds for emergency care of stroke patients.

The study **Group 1** included 40 patients, 10 of them had haemorrhagic stroke, 15 ischaemic stroke, and 15 severe TBI. The inclusion criteria were axillary temperature above 38 °C and the absence of significant infectious complications (leukocytosis below 10 g/L, the number of stabs below 7%). The comprehensive therapy of the hyperthermic syndrome was introduced. In included laying ice packs around the patient's body (craniocerebral hyperthermia and laying the packs on the projection of main vessels in the groin). The solutions given intravenously were cooled. Paracetamol was administered in a dose of 1,000 mg 3 times a day. Temperature reduction was monitored every 20 minutes.

The study **Group 2** included 40 patients, 8 of them had haemorrhagic stroke, 18 ischaemic stroke, and 15 severe TBI. The inclusion criteria were axillary temperature above 38 °C and the absence of significant infectious complications (leukocytosis below 10 g/L, the number of stabs below 7%). Patients in group 2 were also given the comprehensive therapy of the hyperthermia syndrome. Physical cooling was performed similarly to group 1. Acelysin was also administered intravenously in a dose of 1 g 3 times a day. Paracetamol was not administered.

The study **Group 3** included 15 patients with concomitant injury. The inclusion criteria were concomitant injury of two or more anatomical regions with preserved consciousness (GCS 14-15 b). Eight patients with multiple fractures of limbs and 7 patients with fractures of the limbs and thoracic trauma were included. Patients were administered intramuscularly nalbuphine at a starting dose of 20 mg 3 times a day, with subsequent dose adjustments "on demand." Paracetamol was administered in a dose of 1,000 mg 3 times a day.

The study **Group 4** included 15 patients with concomitant injury. The inclusion criteria were concomitant injury of two or more anatomical regions with preserved consciousness (GCS 14-15 b). Nine patients with multiple fractures of limbs and 6 patients with fractures of the limbs and thoracic trauma were included. Patients were administered intramuscularly morphine HCl 1% solution at a starting dose of 1 mL 3 times a day, with subsequent dose adjustments "on demand." Concurrently, 2 mL of Analgin 50% solution and 1 mL of diphenhydramine 1% solution were given intravenously 3 times a day. Paracetamol was not administered.

In groups 3 and 4, patients evaluated the intensity of postoperative pain by a verbal scale (VS), where 0 - no pain, 1 point - mild pain on movement, 2 points - mild pain at rest and moderate pain on movement, 3 points - moderate pain at rest and severe on movement, and 4 points - very severe pain.

RESULTS AND DISCUSSION

When comparing the efficacy of intravenous paracetamol and acelysin on the background of the similar methods of physical cooling of patients, a more rapid and sustained reduction in body temperature was revealed in the paracetamol group. The results of dynamic monitoring of the axillary temperature are shown in Tables 1 and 2.

Table 1 Management of hyperthermia in Group 1

	Baseline body temperature	1 hour after paracetamol administration	2 hours after paracetamol administration	4 hours after paracetamol administration	p
Patients with acute cerebral vascular accident	39.5±0.6 °C	38.4±0.5 °C	38.0±0.6 °C	37.4±0.4 °C	< 0.05
Patients with TBI	39.3±0.5 °C	38.2±0.5 °C	37.9±0.7 °C	37.2±0.5 °C	< 0.05

Table 2 Management of hyperthermia in Group 2

	Baseline body temperature	1 hour after administration of acelysin	2 hours after administration of acelysin	4 hours after administration of acelysin	p
Patients with acute cerebral vascular accident	39.3±0.7 °C	38.9±0.4 °C	38.5±0.6 °C	38.4±0.5 °C	< 0.05
Patients with TBI	39.6±0.5 °C	38.7±0.6 °C	38.4±0.5 °C	38.2±0.4 °C	< 0.05

A comparison of the analgesic efficacy of the combinations nalbuphine/infalgan and morphine/infalgan/analgin revealed a higher efficiency of the former combination. Furthermore, it was observed that the administration of intravenous paracetamol in combination with nalbuphine allowed to reduce the dose of the latter on average by 30% already on day 2, on average by 60% on day 3, and starting from day 4 the need for narcotic analgesics completely disappeared as paracetamol monotherapy was sufficient. In group 4, where paracetamol was not used, a need for narcotic analgesics persisted through 5-6 days.

Table 3

Management of pain in Group 3

	VS, baseline score	30 min after administration of nalbuphine and paracetamol	2 hours after administration of nalbuphine and paracetamol	4 hours after administration of nalbuphine and paracetamol	p
Patients with thoracic trauma	3.8±0.2	3.0±0.3	2.3±0.2	1.9±0.3	< 0.05
Patients without thoracic trauma	3.6±0.3	2.9±0.2	2.1±0.4	1.7±0.2	< 0.05

Table 4 Management of pain syndrome in Group 4

	VS, baseline score	30 minutes after administration of morphine, analgin and dimesol	2 hours after administration of morphine, analgin and dimesol	4 hours after administration of morphine, analgin and dimesol	p
Patients with thoracic trauma	3.8±0.2	3.2±0.3	2.9±0.3	2.5±0.3	< 0.05
Patients without thoracic trauma	3.7±0.3	3.2±0.4	2.8±0.2	2.4±0.4	< 0.05

CONCLUSIONS

1. The use of the intravenous dosage form of paracetamol aimed at managing central hyperthermia in combination with physical cooling methods allows to achieve a clinically significant decrease in body temperature down to safe values, which is more pronounced in comparison to that with acetylsalicylic acid.

2. Intravenous paracetamol used in combination with narcotic analgesics is effective in managing severe pain that is characteristic to concurrent injury, can significantly reduce the dose of opioids and provides an earlier discontinuation of them, which lowers the risk of possible complications due to the long-term use.

3. Paracetamol was well tolerated, with no serious adverse effects being reported. Most physicians and patients rated the efficacy of the treatment and satisfaction with it as "very good" or "good."

LITERATURE

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Address for correspondence:

Volodymyr Ilyich Cherniy, Prof., PhD in Medicine, Corresponding Member with the NAMS, Head of the Department of Anaesthesiology, IC, EM and Laboratory Diagnostics at Donetsk National Medical University n. a. M. Gorky E-mail: vicerecordnmu@yandex.ua