

CAN WE TREAT URGENT MEDICAL CONDITIONS WITHOUT ADEQUATE DRUGS?

*Jokšić-Mazinjanin Radojka (1); Vasović Velibor (2); Gojković Zoran (3); Mikov Momir (2); Mikov Ivan (4)
Aleksandar Đuričin (1); Jokšić Zelić Milena (5); Saravolac Siniša (6)*

(1) UNIVERSITY OF NOVI SAD, MEDICAL FACULTY OF NOVI SAD, CHAIR OF EMERGENCY MEDICINE; INSTITUTE OF EMERGENCY MEDICINE OF NOVI SAD, NOVI SAD; (2) UNIVERSITY OF NOVI SAD, MEDICAL FACULTY OF NOVI SAD, CHAIR OF PHARMACOLOGY, TOXICOLOGY AND CLINICAL PHARMACOLOGY, NOVI SAD; (3) UNIVERSITY OF NOVI SAD, MEDICAL FACULTY OF NOVI SAD, CHAIR OF SURGERY; CLINICAL CENTRE OF VOJVODINA, CLINIC FOR ORTHOPEDIC SURGERY AND TRAUMATOLOGY, NOVI SAD; (4) UNIVERSITY OF NOVI SAD, MEDICAL FACULTY OF NOVI SAD, CHAIR OF OCCUPATIONAL MEDICINE; CLINICAL CENTRE OF VOJVODINA, POLICLINIC, NOVI SAD; (5) PRIMARY HEALTH CARE CENTRE BEČEJ, EMERGENCY MEDICINE DEPARTMENT, BEČEJ; (6) INSTITUTE FOR EMERGENCY MEDICINE OF NOVI SAD, NOVI SAD

Summary: Emergency Medicine does not represent a simple collection of various medical conditions, but rather an urgent approach to life threatening conditions. This urgent approach progresses as fast as the science in medicine does. Modern protocols for treatment of injured and ill patients are introduced, demanding more and more knowledge and skills as well as more modern equipment and wider spectrum of drugs. However, innovations are not followed by changes within the lists of medications set by National Health Insurance Fund of Serbia (NHIFS). Paper describes drugs necessary for adequate pre-hospital treatment that are not available to the physicians due to administrative barriers. On one hand, there are drugs from B list that are necessary for treatment, and are approved for use by NHIFS at hospital level only. The use of any of these drugs at pre-hospital level may lead to severe penalties to the physician in case of complications or adverse reactions in a patient following the treatment. On the other hand, there are drugs from D list which are also necessary for the urgent treatment of patients with life threatening conditions, according to latest recommendations. These drugs may be applied at pre-hospital level, but their procurement is complicated due to NHIFS regulations and that's why some of them may rarely be used (Propafenone and Magnesium sulfate). We particularly emphasize that one of the most effective drugs for the conversion of heart rhythm, Adenosine (6 mg/ml and 10mg/ml ampoule), is not registered in the Republic of Serbia and therefore cannot be used at pre-hospital level. Through these exclusive administrative barriers adequate treatment is rendered impossible while the system of urgent treatment of patients with life threatening conditions at pre-hospital level is degraded.

Key words: Emergency medical care, urgent medical conditions, treatment protocols, drugs

History of the development of Emergency Medicine

Emergency Medicine does not represent a simple collection of various medical conditions, but rather an urgent approach to life threatening conditions. It includes decision making and undertaking rapid measures in order to prevent death or deterioration of an existing life threatening condition in a patient. It is a particular medical specialty the primary task of which is urgent recognition, treatment and prevention of unexpected life threatening illness or injury in a patient. [1]

Emergency Medical Care (EMC) is a special area of health care arranged at primary health care level, organized in order to undertake necessary and immediate medical interventions so that deterioration or permanent damage caused by life threatening conditions could be avoided. [2] Unlike the First Aid measures provided by a layman, in our settings Emergency Medical Care is provided by a health professional specially trained for the treatment of these conditions

First records on provision of EMC were detected on papyrus dated 700 years B.C. Further historical records from various periods in time clearly show that EMC was present and

available with various types of organization and was improved through centuries. In 1955 external defibrillator was used for the first time and in 1958 artificial ventilation (mouth to mouth) was described followed by description of external heart compression in 1960. However, EMC was still provided by interns, physicians with other medical specialties and hastily trained staff at that time. Introduction of innovations in pre-hospital treatment of injured and ill patients lead to the development of separate medical specialty –urgent medicine. First Chair of Urgent Medicine was founded in 1971 at Medical Faculty in California. [3,4,5,6] In Former Yugoslavia, first Chair of Urgent Medicine was founded in 1979 at Medical Faculty of Sarajevo. Much later on, in 1991, Chair of Urgent Medicine was founded at Medical Faculty in Belgrade, followed by Medical Faculties in Nis, Novi Sad, Ljubljana and Zagreb in 1993, 1994, 2007 and 2010, respectively.

Implementation of protocols for treatment of life threatening conditions was as quick as was the progress of Urgent Medicine as a separate medical specialty. One of the first protocols implemented during the 70s of the XX century, was the so called Advanced Cardiac Life Support protocol. [7] After that, protocols for the treatment of trauma in the field settings, acute myocardial infarction, acute stroke, periarrest arrhythmias and many other were introduced. [8,9,10,11,12] Evidence based protocols are being updated annually. Urgent Medicine specialists are trying to implement new protocols in Serbia that have not been used previously. [13] Improvement and use of new protocols necessitates provision and use of modern equipment and wider spectrum of drugs. However, National Health Insurance Fund of Serbia (NHIFS) annually sets the lists of registered medications that they will cover for. [14] Innovations in treatment of life threatening conditions are not followed by changes within the official lists of medications set by NHIFS, which may lead to lower quality in treatment compared to the best recommended one.

There are five official lists of medications set by NHIFS:

- A List – Drugs prescribed by physicians and issued based on official physician's prescription form
- A1 List - Drugs prescribed by physicians and issued based on official physician's

prescription form, which have therapeutic parallel to the drugs from A List

- B List – Drugs issued on order and applied during a treatment in outpatient clinics or hospital

- C List – Drugs with special regime of prescribing

- D List – Drugs without a license for use in Serbia, but necessary in diagnostic and therapy – unregistered drugs [14]

B and D lists contain drugs which are necessary for pre-hospital treatment of patients according to latest recommendations, but which are, for various reasons, unavailable to urgent medicine physician working in the departments for EMC.

Drugs from the B List unavailable for pre-hospital treatment

A total of nine drugs necessary for pre-hospital treatment are currently on the B List and their use is exclusively allowed in hospital facilities. These are:

Pantoprazole, 40mg, bottle
 Streptokinase, 1.500.000 units bottle
 Hydroxyethyl starch, Sodium chloride 6% 500ml bottle and 10% 500ml bottle
 Urapidil 25/5ml or 50mg/10ml ampoule
 Oxytocin 5 or 10 IJ/ml ampoule
 Propofol 10mg/ml ampoule
 Midazolam 5mg/5ml or 15mg/3ml ampoule
 Flumazenil 0,5mg/5ml or 1mg/5ml ampoule
 Protamine sulfate, 50mg/5ml bottle

First drug from the B List, unavailable for pre-hospital treatment is Pantoprazole. Gilbert and associates in 2001 published a meta-analyses on comparison of efficacy of proton pump inhibitors versus H₂ antagonists in patients with bleeding gastric ulcer. Results showed that the use of proton pump inhibitors reduces the risk of long-term and repeated bleeding from gastric ulcer. [15] Intravenous drug administration almost instantly causes reduction of acidity of gastric content, preventing further damage at the sight of ulcer niche. [16,17] Masjedizadeh and associates conducted a prospective randomized study in 2014 and concluded that the use of Pantoprazole is equally efficient regardless of whether the dosage was high (80mg during the first hour, followed by 8mg/h the next three days) or low (40mg during the first hour, followed by 4mg/h the next three days) and administered as continuous intravenous infusion. [18] This clearly showed the need for the use of proton pump inhibitors as soon as

possible in patients with bleeding ulcers in gastrointestinal tract. In our settings, ampoules are available only at hospital level, so that in vast majority of cases drug cannot be used during the first hour of bleeding when the patient is far away from the hospital. The use of Ranitidine in these situations is inadequate substitute for the use of Pantoprazole and therefore bleeding is prolonged, patient's condition deteriorated and in some cases life threatening.

Plasma expanders Hydroxyethyl starch, Sodium chloride 6% and 10%, so called Hetasorb®, are a group of drugs that are also unavailable for pre-hospital use. In case of hypovolemic shock when compensation of volume is necessary, solutions of sodium chloride are needed and these are also unavailable and are not on any of the lists issued by NHIFS. According to the National Guidelines for good clinical Practice, issued by the Ministry of Health of Serbia, Ringer Lactate, 0,9% NaCl is recommended for pre-hospital diagnosis and treatment of urgent medical conditions for compensation of volume in hypovolemic shock and hypertonic solution is a third option [19]. Fluid compensation is the first therapeutic measure in trauma patients with hypovolemic shock. There is no evidence from the literature showing that fluid compensation is better with one type of solution than another. Advantage of colloids is faster and more long-term maintenance of volume of circulating fluid, absence of tissue edema or acid base status disorder. [20] Advantage of hypertonic salty solutions is quick increase in circulatory fluid volume. They are most valuable when used together with colloids. [21] Team for EMC is the first responder to severely injured patients. In case that team has no colloids or hypertonic salty solutions at their disposal when dealing with the injured patient in pre-hospital settings, they can undertake all necessary measures to preserve life of trauma patient with hypovolemic shock. [22]

Urapidil is another drug that is missing for pre-hospital use. This drug is also on the B List, but can be administered only in hospitals settings. Urapidil administration is most important in case of preeclampsia. It reduces blood pressure in 80% of cases when used as isolated drug intravenously. It has no adverse effects on the mother or child. However, if used too fast it can cause hypotension. [22,23] Use of this drug is justified in hypertension crisis as

well as in a case of ischemic and hemorrhagic stroke with hypertension crisis. [24] Drug is not available for pre-hospital use just like Sodium nitroprusside or Labetalol which are recommended by National Guidelines of Good Clinical Practice for pre-hospital diagnosis and treatment of urgent medical conditions issued by the Ministry of Health. Therefore, there is no possibility of adequate care in case of hypertension in preeclampsia.

Oxytocin is another drug missing in pre-hospital care of urgent medical conditions in gynecology and obstetrics, besides Urapidil. It can be used in pre-hospital settings during the third labor age in order to shorten the period of expulsion of the placenta, consequently reducing the blood loss. Besides that, it can be used in infusion of crystalloids in case of heavy bleeding after delivery. [19,25] Abundant bleeding after delivery represent urgent medical condition when over 500 ml of blood is lost. Frequently, place of delivery is remote from adequate hospital facility. In case of expulsion of the placenta after delivery or if the bleeding is abundant, lack of oxytocin in pre-hospital settings may represent a big problem.

Propofol is also one of the drugs unavailable for pre-hospital use according to the NHIFS. Its administration is limited to the hospital settings. Propofol is a general anesthetic used intravenously for the induction and preservation of general anesthesia, sedation of the patient during mechanical ventilation and other diagnostic and therapeutic procedures. It has sedative, hypnotic, anticonvulsive and antiemetic characteristics. It is recommended for sedation before intubation in patients with severe asthma particularly if bronchospasm is expressed. [26,27,28] Propofol is recommended in patients with severe cranial injuries without hypovolemic shock in order to reduce intracranial pressure. [29] Mackay and associates published the research in 2001 showing that urgent medicine physicians are equally capable as anesthesiologists to take care of and intubate a patient in short term anesthesia. Therefore, urgent medicine physicians can safely use intravenous sedatives and neuromuscular blockers in pre-hospital settings. [30]

Midazolam is reserved for the use in hospital settings and is also on the B List, although the most EMC departments in Serbia have this drug at their disposal. In case of pre-

hospital use followed by complications or adverse events in a patient receiving the drug, physician may be exposed to severe judicial penalties. Midazolam is a benzodiazepine with sedative, hypnotic, anticonvulsive and muscle relaxation characteristics. Sedative and hypnotic effects occur quickly and last shortly, making this drug a good choice for short term sedation when pre-hospital intubation is difficult. [26, 31] Edward and associates conducted a research in 1999 showing that the use of this drug is justified in pre-hospital settings when intubation is difficult and also if performed by paramedics. [31] Considering the fact that in our country urgent medicine physicians work in pre-hospital settings there is no justification for the exclusive use of Propofol and Midazolam there. The two remaining drugs will be described in a separate chapter due to the fact that they are antidotes, a group of drugs extremely important for pre-hospital use in urgent medical conditions.

Drugs from the D List unavailable for pre-hospital treatment

Drugs from the D List, necessary for urgent medical care in life threatening conditions can be divided in two groups. The first group is comprised of drugs unregistered in Serbia, but available in EMC departments. These are: Atropine sulfate, Aminophylline, Glucose 50% and Naloxone hydrochloride. The second group is comprised of drugs that are unavailable but necessary for work in EMC. These are Propafenone ampoule 35mg/10ml and Magnesium sulfate 20%, 100 ml. bottle. Propafenone is member of Ic group of antiarrhythmics. It blocks sodium channels leading to slowing down the heart rhythm. It is used for therapy of supraventricular and ventricular tachycardia, and the most significant use is for therapy of Wolf-Parkinson-White syndrome. [32] Lately, it has been more frequently used in pre-hospital settings for conversion of atrial fibrillation, lasting less than 48 hours, into sinus rhythm. It is equally efficient as Amiodarone, but provides the effect faster. [33] It is equally efficient for the control of speed of ventricular response in case of fast supraventricular arrhythmias. [34]

Regardless of excellent recommendations it is not registered in Serbia so that it is not available to urgent medicine physicians for pre-hospital use.

Just like Propafenone, Magnesium sulfate is not available either. This drug is used during pregnancy in case of preeclampsia, eclampsia or intoxication for the prevention of convulsions. [35] It is also recommended in case of Torsades des pointes prolonged Q-T interval. [36] Intravenous administration is justified in case of severe asthma attack. [37] All of these are life threatening conditions where adequate therapy is needed as soon as possible. Delay in provision of proper therapy especially in case of eclampsia with convulsions may have fatal consequences in a pregnant woman or offspring. This is the reason why Magnesium sulfate should be provided to EMC teams for pre-hospital use.

Unregistered drugs in Serbia, not present on any of the lists

There are drugs unregistered in Serbia and not recognized by NHIFS as necessary for therapy neither at pre-hospital nor at hospital level. These drugs are not present on any of the lists issued by the NHIFS despite the fact that Global or European recommendations consider them necessary in certain urgent medical conditions. These are:

Adenosine, 3mg/ml ampoule

Biperiden, 5mg/ml ampoule

Carbo medicinalis (tablets, granules or suspension in sorbitol).

Adenosine is an antiarrhythmic. It is efficient for conversion of supraventricular tachycardia into a sinus rhythm. It represents first choice among drugs for the therapy of supraventricular rhythm disorders as stated in the recommendations from 2003, as well as in the recommendations from 2010 when periarrest arrhythmias are considered. [38,39] It was recommended by the Working Group for the creation of National Guidelines for Good clinical Practice in pre-hospital diagnostic and treatment of urgent medical conditions. [25 40] Adenosine acts faster, has shorter effect, is safer for use in pregnancy, has less adverse events than other antiarrhythmic drugs. [38,41,39] Gausche and associates published the study in 1994 showing Adenosine effective and safe to convert supraventricular tachycardia in pre-hospital use by paramedics. [42] This means that there are no limits for the procurement of the drug and its pre-hospital use by urgent medicine physicians.

Biperiden is the second unregistered drug. It is anticholinergic that is used

intravenously in therapy of: Parkinson disease (especially for rigors and tremors), iatrogenic extrapyramidal syndrome, nicotine poisoning and poisoning caused by organic compounds of phosphorus. [43] Having in mind the fact that EMC teams use Haloperidol in pre-hospital settings to treat various agitated states and also deal with intoxications with expressed extrapyramidal syndrome, Biperiden (for intravenous use) availability is necessary. The remaining drug is an antidote and will be described in separate chapter.

Antidotes

Antidotes physically or chemically react with toxic substance or pharmacologically and biochemically correct the disorders caused by toxic substance that entered the organism. Antidotes are divided into specific and non-specific. Specific antidotes act on certain toxic substance while non-specific have neutralizing effect on a large number of toxic substances. [43,44] Principles of pre-hospital care of an intoxicated patient are summarized as ABCDE approach, followed by detoxification that encompasses prevention of toxic substances absorption, acceleration of its elimination, and the use of antidotes. [40,43,44] First two measures in detoxification may be applied, while the third one, use of antidotes, is most frequently unavailable in pre-hospital settings. Intoxications occur in farmers working in remote areas far away from hospitals. Time of the transport in such cases is significantly longer than usual and EMC teams are not in the position to undertake all the measures so that life could be saved and damage to the vital organs reduced to a minimum. [45] Some antidotes are unavailable such as:

Flumazenil, 0,5mg/5ml or 1mg/5ml ampoule

Protamine sulfate 50mg/5ml bottle

Glucagon syringe 1mg/1ml.

Carbo medicinalis (tablets, granules or suspension in sorbitol).

Flumazenil is specific benzodiazepine antagonist used in case when the effect of benzodiazepine needs to be reduced or interrupted quickly. [26,46] This drug has a short half-life of elimination, around an hour, so that after the initial dose slow intravenous infusion has to be continued. It is very efficient in benzodiazepine overdose, but it is not recommended in mixed intoxications or as a

routine drug in differential diagnosis of coma. [47,48] It is indicated for hemodynamically stable patients who received or deliberately took high doses of benzodiazepines. In such a case, the drug has low frequency of side effects and is considered safer than intubation and mechanical ventilation in patients whose breathing is compromised. [46,47,49] This drug is on the B List, however its use is reserved for hospitals.

Protamine sulfate is also a specific antidote. This drug is used in case of heparin overdose. It is efficient in case of overdose by non fractionated and low molecular heparin. It is applied when heavy bleeding occurred after heparin overdose. Therapy should be started immediately in order to stop the bleeding and reduce the risk of death. [26,50] This drug is not registered in Serbia and is on the D List, so that it can be procured for special indications only

Glucagon is also unavailable for pre-hospital use. This drug is applied in case of hypoglycemia and as a specific antidote in case of β -blocker and calcium channel antagonist intoxication. [26] In case of β -blocker intoxication the drug is applied in high dosage as an antidote of first choice, while in case of calcium channels antagonist intoxication it can be used only in extremely difficult cases when recommended antidotes become ineffective. [51,52] β -blocker intoxication do not occur frequently, but are potentially life threatening requiring urgent use of antidotes. High doses applied intravenously may be life saving. [53] Glucagon is on the A List so it is available to the EMC teams.

Beside specific ones, Carbo medicinalis as an unspecific antidote is also unavailable. Prevention of toxic substances absorption has an important and unavoidable role in the process of treatment of intoxicated patients. Potential benefit of Carbo medicinalis use in cases of intoxication is well known since the 1830s. During the last twenty years its use has been essential in case of intoxication occurred within one hour. [53,54,55] A team of EMC arrives at proper location of the incident most frequently within one hour. However, additional time is needed for pre-hospital treatment and transport to a hospital facility so that one hour is frequently exceeded. Greater benefit could be achieved in case of Carbo Medicinalis availability to EMC teams for pre-hospital care because within one hour complete absorption of the toxic

substance in the digestive tract would be prevented.

CONCLUSION

Emergency Medical Care most frequently deals with life threatening conditions. Due to unavailability of certain drugs there is no

possibility of adequate treatment according to modern protocols. Through administrative barriers created by making drugs unavailable or allowed for exclusive use at hospital level, adequate treatment is rendered impossible, while the system of urgent treatment of patients with life threatening conditions at pre-hospital level is degraded.

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