Review paper

Analgetic and sedative agents administered to the patients in life-threatening conditions

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Abstract

Pharmacotherapy implemented to the patients who are in the life-threatening condition should be carried out in a quick and prepense way. The general condition of the patients in this state, after being administered strongly effecting drugs such as analgesics and sedatives may become not better but worse. In the following work the authors presented the modern approach and methods of administering analgesics and sedatives (including general intravenous anaesthetics) to the patients who sustained injuries as a result of a car accident. The authors presented opioids and non-steroid anti-inflammatory drugs, considering their administration prior to full access to the victim. They also discussed the risk connected with administration of strongly effecting drugs and indicated the interactions between administered substances.

Key words: analgetic agent, sedative agent, life-threatening conditions.

The progress of motorization has lead to the increasing number of traffic accidents. Modern safety measures used in the car cabins have improved the safety of the driver and passengers, but not (for reasons which can be understood easily) that of the pedestrians who are seriously injured more and more frequently. The drivers and passengers, in turn, become the victims of acceleration resulting from sudden braking, even if they are not injured by the elements of the damaged car [1].

The victims of accidents sometimes present with psychomotor agitation, which makes basic procedures, such as vein cannulation, impossible to perform. Such a condition usually results from hypoxia, due to various causes, e.g. pneumothorax, pain, hypovolemia, airway obstruction or increased intracranial pressure, but also to stress. Hypoxia can be treated under emergency conditions by oxygen administration. It should be realized that the victims of accidents are unable to assess their state. If it is aggravating, or if it can become worse, the patient's vein should be cannulated as soon as possible to enable the commencement of treatment.

The physician deciding to use analgesia and sedation should take into consideration the potential risk associated with these methods.

There is a group of physicians, mainly working in the surgical, orthopedic and neurosurgery wards, who oppose using opiates and sedation within the framework of emergency aid rendered to accident victims. In their opinion, the effects of such medication "obscure the picture of the disease". Treatment of pain and possible induction of sedation is an integral part of emergency management of the victim. The transport of the patient with injuries, leading to traumatic shock can do much more harm; the effects of catecholaminemia can e. g. in patients with concomitant coronary heart disease lead to myocardial infarction (due to tachycardia and myocardial oxygen deficits). Additionally, the emergency service physician's decision to administer any drugs should involve precise assessment of the patient's condition (both clinical and neurological). The modern diagnostic methods allow to assess the injuries accurately without the need to maintain the patient's consciousness (patients suffering from severe pain is not a reliable source of information concerning the extent of injury). It seems that the following principles should be followed in the management of accident victims [2, 3].

The contraindication for administration of opiates and sedatives should be the possibility of causing respiratory depression and consequent hypoxia. This could be prevented by employing ONLY anesthesiologists in the emergency teams (and in future also physicians specialized in emergency medicine) who are the most experienced in detection and management of respiratory failure [3, 4].

Similarly, a reduced dose of an opioid analgesic administered to the patient may be more harmful than a full dose sufficient to control pain (e.g. to control pain caused by scalds and burns, a dose exceeding several-fold the recommended clinical dose is sometimes necessary).

In acute traumatic pain, we have to deal with two of its components:

1. Baseline pain (present both at rest and during simple movements and procedures).
2. Pain associated with specific procedures, such as dressing the wound and immobilization, manipulations within the wound, etc.

Noxious stimulation from the damaged tissues is massive and tremendously stressogenic at that time.

The fundamental aim of the treatment is to maintain systemic homeostasis. The duration of this stage usually does not exceed 72 hours.

Opioid agents play an important role in analgesic management of the patients with traumas. The prerequisite for their use is the presence in the emergency team of an experienced physician, preferably an anesthesiologist. In order to obtain quick and effective opiate analgesia, it is necessary to achieve therapeutic concentration of the drug in the blood and to maintain it throughout the whole time of the therapy. The main route of drug administration under emergency conditions is intravenous infusion, ensuring:

- Instant therapeutic effect (for piperidine derivatives the latency time (from administration to the manifestation of effect) is ca. 2 min.
- Reliable systemic distribution (within the central compartment); the patients in shock demonstrate impaired absorption of drugs from the muscular and subcutaneous tissue due to centralization of the circulation.
- Almost immediate onset of side effects, which can be promptly counteracted [5].

The treatment of pain commences with the administration of a saturating dose, which is followed by subsequent single (bolus) doses or continuous intravenous infusion. The saturating dose can be also administered by a route other than intravenous. When a satisfactory analgesic effect is obtained (after the saturating dose), it should be maintained by regular administration of maintenance doses at appropriate intervals based on the pharmacodynamics of the preparation, the patient's body weight and subjective pain sensation. Analgesic agents should be administered even if after the initial dose the patient does not report any pain. This prevents the fall of the therapeutic blood level of the drug. Administration of analgesics at regular intervals consistent with the pharmacodynamics of the drug results in reduction of the patient's demand for analgesics (higher doses are needed to treat pain than to prevent it). Continuous intravenous infusion of opiates is a relatively simple technique of pain management, which is often forgotten nowadays. The initial, saturating dose is determined by titration (small consecutive doses are administered until pain subsides), and then the therapeutic (analgesic) concentration of the drug is maintained by its continuous intravenous infusion. The infusion rate can be approximated by a simple calculation based on two principles:

In emergency situations, mainly opioid agents characterized by the short-term effect are used. This group includes some piperidine derivatives (fentanil, alfentanil, sufentanil and remifentanil). They are quickly eliminated from the organism, do not accumulate, so their dosage can be controlled easily and their potential side effects subside in a short time. The above preparation causes a negligible – clinically insignificant – histamine release. Opioids are characterized by the occurrence of side effects, the most important of which (from the point of view of emergency management) is respiratory depression.

It is dose-dependent and increases with higher doses. It reaches its peak ca. 7 min after intravenous injection, ca. 30 min after intramuscular, and ca. 90 min after subcutaneous administration. Respiratory depression is characterized by insensitivity of the respiratory center (located in the brainstem) to pCO_2 increase. Respiratory depression caused by opioids can be reversed by administration of an opiate antagonist (naloxone at 1-3 µg/kg b.w. dose, 0.4 mg/1 ml ampule). However, it should be taken into consideration that besides respiratory depression also the analgesic effect is abolished by naloxone (and it cannot be restored by administration of another opioid). Thus, the principle should be followed that if pain can be controlled by administering high doses of opioids which may cause respiratory depression, general anesthesia should be induced, the patient should be intubated and artificially ventilated (connected to a respirator or ventilated with a resuscitator eg. an AMBU bag) [6-8].

Sometimes the emergency team at the site of the accident encounters problems with vein cannulation (obtaining intravenous access). In children, a useful technique in such cases is puncture of the marrow cavity in the tibial bone. In the Christoph 22 programme conducted in Germany, it was established that crystalloids, colloids, adrenaline, ketamine, thiopental, diazepam, scoline and vecuronium can be administered into the bone.

To date, the use of non-steroid anti-inflammatory agents in post-traumatic analgesia has been limited due to their pharmacological properties.

These disadvantages are balanced by the fact that it is impossible to develop psychical or physical (practically insignificant in emergency situations) tolerance to these drugs. Recently, a paracetamol in the form for intravenous injections (Perfalgan BMS) has appeared in the market. The preparation is available in 1 g ampules. The studies of a derivative of carboxylic acid with pyrolacetic acid – Ketolorac tromethamine (Tora-Dol; Syntex Pharma; 0.03/1 ml amp., 0.01 tabl.) – are very promising. Mean half-life time after intramiscular injection is 5.4 h (thus, it is relatively long). Elimination of the drug takes place predominantly through the kidneys. No potentially dangerous interactions with other drugs have been described. The preparation is indicated particularly in the cases of acute pains associated with post-operative conditions, traumas due to accidents such as spraining and dislocations of the joints, etc. Tora-Dol should not be used in patients with diagnosed hypersensitivity to ketolorac, with active peptic ulcers, in subjects below 16 years of age, and in those in whom the serum creatinine level does not exceed 5 mg/dL. The preparation is administered intravenously or intramuscularly at the 0.03 single dose; a daily dose of 0.120 (4 ampules) should not be exceeded. IM or IV administration of 30 mg of the preparation induces analgesia equivalent to 10 mg morphine [9].

Some authors support the concept of nerve trunk blockades performed within the framework of emergency service, or even of blockades of the central type, i.e. subarachnoid (epidural). The authors from the West are a little more cautious, stating that the first absolute contraindication for such method of management is the lack of consent expressed by the patient, whose consciousness may be considerably impaired as a result of the accident.

Additional caution must be taken because of the impossibility to obtain a complete picture of the patient's injuries and the lack of appropriate aseptic conditions and monitoring necessary for such types of anesthesia (the patient after subarachnoid anesthesia transported in an ambulance, speeding along uneven roads?). There have been, however, successful clinical trials involving IV segmental analgesia (0.5% lidocaine solution, 1 µg/kg b.w. fentanil and 0.5 mg pancuronium) used in the cases of upper extremity injuries.

Acute pain may have a considerable influence on the patient's mental condition, who is afraid of losing control of his emotions, as well as of the pain becoming intolerable. Pain causes anxiety and anxiety increases the intensity of pain. There is a linear correlation between pain and anxiety; the more intensive the pain is, the more anxious the patient becomes. Higher anxiety prompts the patient to demand higher doses of analgesics. The drugs commonly used to support analgesia are those belonging to the group of benzodiazepines which are beneficial to control anxiety accompanying acute pain. The anxiolytic effect of all benzodiazepines is similar and involves enhancement of neuronal inhibition, whose neurotransmitter is gamma-aminobutyric acid (GABA). The most commonly used benzodiazepine is diazepam. Because of long half-life time of diazepam and its active metabolites, the effect of high doses may be maintained very long. It is administered in 0.1-0.2 mg/kg b.w. doses, but it should not be used in emergency situations because of the aforementioned properties. Diazepam is the most potent anticonvulsant (in comparison with other benzodiazepines). Midazolam (Dormicum, Versed) is a preparation well soluble in water, characterized by rapid onset and short duration of effect, causes anterograde amnesia, and the lack of active metabolites makes it useful for continuous IV infusions. However, similarly as in the cases of other drugs with short-term effect, midazolam is accumulated in the tissues. Midazolam is administered in 0.1-0.3 mg/kg b.w. doses, and 0.0.5-0.3 mg/kg b.w./h doses are used for continuous IV infusions. The side effects associated with benzodiazepine medication include asthenia, headaches, blurred vision, vertigo, nausea, vomiting and diarrheas. It should be remember that benzodiazepines, acting on the central nervous system,

may potentiate respiratory depression caused by opiates. All the drugs of this group may cause paradoxical effect, especially if they are administered at high doses for a long time. Combined medication with benzodiazepines and opioids is referred to as tranquanalgesia and requires reducing the doses of both drugs. Benzodiazepines have a specific antagonist – flumazenil (Anexate), which should be used to restore consciousness when we want to assess the general condition of the patient. Administration of flumazenil is also the measure taken in cases of benzodiazepine overdose; the failure to restore consciousness practically excludes the possibility to use drugs of this group in the patient. The preparation is administered in 15-20 µg/kg b.w. doses, intramuscularly or intravenously.

There are also other drugs used in general anesthesia which can be also used to induce sedation at lower doses than those needed to obtain an anesthetic effect. They should be administered by titration after careful consideration of indications.

They include etomidate, propofol (warning: it abolishes pharyngeal and laryngeal reflexes), as well as barbiturates (methohexital, thiopental). However, these drugs should be administered only by anesthesiologists because of the adverse effects they may cause. Except for etomidate, these drugs have a potent cardiodepressant effect and they should not be used in hypovolemia.

The plausibility of nitrous oxide administration in an emergency situation is discussed. The low value of the blood/gas index characteristic of this anesthetic causes rapid induction of analgesia, but also rapid elimination from the organism when its administration is discontinued. Nitrous oxide administered in 50% concentration together with oxygen (in 1:1 v/v ratio – Entonox) causes analgesia equivalent to that induced by 10 mg IM morphine. However, the potential hazards associated with its use should be taken into account. Besides bone marrow suppression (evident already after 1 h administration to patients in shock), teratogenic effect, induction of nausea and vomiting (sympathicomimetic effect) nitrous oxide causes diffusion hypoxia (fink phenomenon). After the termination of anesthesia, large amounts of nitrous oxide are eliminated from the tissues to the blood and from the blood to the lungs (nitrous oxide is soluble in plasma 34 x better than nitrogen). As a result, expiratory volume exceeds inspiratory volume; larger volumes of CO_2 are eliminated from the organism than in physiological conditions, which attenuates the respiratory drive due to hypocarbia. A complication caused by massive passage of nitrous oxide to the alveoli is a decrease of actual oxygen concentration (in alveolar gases). Physiological oxygen concentration in alveolar gases amounts to 14%; after the termination of anesthesia it very often falls as low as 10%, which leads to profound hypoxia. Nitrous oxide passes to closed spaces filled by air (the space formed as a result of pneumothorax, distended intestines, air bubbles in the cranial cavity) and increases their volume (as well as gas pressure). The gas present in the pleural cavity expands 15 times more rapidly than the gas trapped in the intestinal lumen. Thus, the presented facts call for very cautious use of nitrous oxide in emergency situations [9, 10].

Ketamine (Calypsol, Gedeon Richter, 20 ml vials; 1 ml=0.05; Ketanest Parke-Davis, 10 ml vials; 1 ml=10 or 50 mg) was introduced as an agent inducing the so-called dissociated anesthesia. It has been established that ketamine administered in subdissociation doses is an effective analgesic. A single IV dose of 0.1-0.4 mg/kg b.w. raises the threshold for experimental noxious stimuli to a level equivalent to the effect of 1 mg/kg b.w. petidine administration. In clinical conditions, it results in a satisfactory level of analgesia, which persists for ca. 60 min, in 80% of patients. Trials concerning the effect of continuous IV infusion have demonstrated that although the level of analgesia is lower than that obtained as a result of opioids, the drug has not such a potent suppressive effect on the respiration center. Ketamine also has the slightest suppressive effect on the cardiovascular system, in comparison with the above mentioned drugs. It has some direct depressive (negative inotropic) effect on the myocardium, but, as it releases catecholamines, it consequently causes an increase of their serum level (indirect effect), so it is responsible for a moderate degree of cardiac stimulation. Ketamine is a preparation which can be administered in subanesthetic (analgesic) doses, i.e. 0.2-0.5 mg/kg b.w. to the casualties trapped in damaged vehicles. The prerequisite for its use is that the patient should be conscious, it should be accompanied by monitoring of vital signs, oxygen therapy and prevention of hypothermia. The hallucinogenic effect of ketamine in response to external stimuli is negligible in the case of analgesic doses (it is absent then; the only sign notable after its administration can be, besides analgesia, the presence of nystagmus appearing when the patient looks sideways). It is also the drug of choice in the treatment of burns. The proposed ketamine doses for continuous IV infusion are preceded by the initial dose of 1 mg/kg b.w. and amount to 3-4 mg/kg b.w./h. According to Kortill (1978), a 0.5 mg/kg b.w. ketamine dose can be combined with 0.15 mg/kg b.w. dose of diazepam. According to White (1982), continuous ketamine infusion should be delivered at a 5-20 µg/kg b.w./min rate after a preliminary saturating dose of 0.2-0.75 mg/kg b.w. It should be remembered that although ketamine can be used as a short-term effect analgesic, there are a number of side effects which impose limitations on its use. They include excessive level of sedation, delirium attacks, hallucinations which

usually occur after anesthetic doses. The incidence of adverse effects can be reduced by combining ketamine with opioids, benzodiazepines, atropine, or – with extreme caution – with neuroleptics. Repeated doses of ketamine may result in the development of tolerance of the drug (tachyphylaxia). Ketamine (administered during the first two hours after trauma) has a beneficial, protective effect on the CNS, despite the fact that it causes an increase of the cerebral blood flow; it is connected with non-specific blockade of NMDA (N-acetyl, D-aspartate) receptors, which, binding the excitatory amino acids, lead to the phenomenon of the so-called central sensitization. Recent studies have been investigating the possibility of combining some agents whose administration to the patients with head injuries will have a protective effect on the CNS; the trials involving joint administration of propofol, ketamine and muscle relaxants enabling mechanical ventilation and maintenance of normocapnia are promising [1, 2, 11].

In intravenous administration of drugs, the organ injuries and/or load on particular systems must be taken into account. Opioids, etomidate and ketamine can be used safely in circulatory failure; however, barbiturates and propofol should not be used. In hepatic failure, fenentanil, morphine and midazolam can be administered, whereas alfentanil, diazepam and ketamine are contraindicated. Renal failure is an indication for reduction of doses of all the used drugs. In patients with injuries involving the CNS, opioids, etomidate, barbiturates, benzodiazepines and propofol can be used, but ketamine and flumazenil should not.

The decision to sedate the patient should be taken with caution, considering all the benefits that can be gained by using such a model of management. The method used to assess the depth of sedation, allowing to differentiate it from aggravation of the patient's condition, resulting from the primary trauma and secondary injuries, should also be selected. It seems that the sedation scales developed by Ramsey and Addenbrooke are relatively simple and effective.

Emergency anesthesia is induced after preliminary diagnostics and requires, besides monitoring vital signs, compensation of any abnormalities and treatment of shock. General anesthesia with inhalation anaesthetics and oxygen-supplemented air mixture used as a carrier is preferred. The recommended inhalation anesthetics are those with low blood/gas partition coefficient (short time of induction and awakening):

- desflurane – 0.4;
- sevoflurane – 0.6;
- isoflurane – 1.4, which are metabolized in the system only in a low degree.

The induction of anesthesia can be inhalatory (overpressure) or intravenous. Preparations administered IV seem to be the drugs of choice in acute hypovolemia. They include benzodiazepines, ketamine, etomidate and propofol. The trachea should be intubated using the following medication:

- Succinylcholine (relaxation is obtained after 52 s);
- Rocuronium (Esmeron, Zamuron) – relaxation is obtained after ca. 65 s; (these preparations are preferred because of short duration of the induced relaxation, which is the essential component of "anti-choking" prevention);
- Mivacurium (Mivacron) – relaxation is obtained after ca. 120 s after a 0.25 mg/kg b.w. dose;
- Ahypnotic only;
- Local (superficial) anesthesia as an alternative.

The anesthesia MUST be induced observing the principles of the so-called "anti-choking" prevention.

Muscle relaxation is obtained by administration of relaxants with non-depolarizing properties:

- Atracurium: 0.3-0.6 mg/kg b.w., continuous infusion 0.3-0.6 mg/kg b.w./h;
- Vecuronium: 0.08-0.1 mg/kg b.w., continuous infusion 0.08-0.1 mg/kg b.w./h;
- Mivacurium: 0.15-0.2 mg/kg b.w.;
- Rocuronium: 0.6 mg/kg b.w., thus, not inducing (in clinically significant doses) histamine release and sympathetic blockade, leading to hypotensia.

Analgesic management can also involve epidural administration of local anesthetics (only after compensation of hypovolemia) or/and opioids. This technique can be combined with general anesthesia – in such cases it is referred to as blended anesthesia. The advantage of this method is that it enables to conduct post-operative analgesia.

In conclusion, it should be stated that there are no universal methods of analgesic management and sedation that could be used in the victims of road accidents. All the agents used in such cases can be classified as representatives of several groups of drugs.

Professional aid rendered to accident victims should involve giving them the comfort of analgesia, enabling the victim to go through diagnostics, transport and surgical treatment. Their consciousness should also be limited until their general condition improves. Although the administration of the aforementioned drugs is associated with the risk of complications and adverse effects, which should be realized, but which can also be prevented and counteracted with increasing efficacy as we gain more experience in the management of this group of patients [12].

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