

PHARMACOLOGICAL MANAGEMENT OF THE POLYTRAUMA PATIENT. ON ANALGESIC THERAPY GUIDELINES

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ABSTRACT

In consideration of the constant, if not increasing number of polytrauma patients arriving in emergency rooms, the pharmacological treatment of pain is a topic that is always under observation and innovation. Even more important is the global management of pain in the polytrauma patient, i.e. its treatment in the phases even after hospitalisation. The existence of pharmacotherapeutic protocols is today an aid for the physician in order to act in the most appropriate way in the shortest possible time. This brief commentary is intended to be a practical guide to the analgesic treatment of the polytrauma patient, in the light of the most recent scientific evidence.

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1. Introduction

The use of drugs in the treatment of different diseases has always been of enormous importance. Just think of the use of anti-SARS-CoV-2 vaccines that, together with the implementation of correct and appropriate prevention and protection procedures [1-4], were able to cope with the pandemic emergency by slowing its progression and reducing the number of hospitalizations [5-6].

In clinical practice, more often than not, the physician has the opportunity to take a careful anamnesis of the patient in order to establish a suitable drug therapy to resolve the disease and/or slow down its progression, as in the case of drugs prescribed for the treatment of neurodegenerative diseases [7]. However, there is not always the possibility of taking a detailed anamnesis of the patient due to the patient's particular emergency conditions.

In such cases, the physician has guidelines rather than treatment protocols at his disposal to ensure a prompt and appropriate drug therapy aimed at the recovery of the patient's vital functions [8].

This could be the case of a professional sportsman or worker who, following an injury, arrives at the hospital emergency room with two or more injuries simultaneously, often associated with the impairment of one or more vital functions [9-11]. In this case, there is little time to think, and useful drugs must be administered quickly to resuscitate the patient.

The presence of two or more traumas at the same time, 'polytrauma', is a clinical condition that can lead to physical, psychological, or other psychosocial damage. One of the most frequent manifestations of polytrauma is traumatic brain injury (TBI) [12,13]. It often occurs in polytrauma and disabling conditions, including amputations, hearing and visual impairments, spinal cord injuries, oxidative stress phenomena and post-traumatic stress disorder [14-21].

It is also interesting to recall how the frequency of work-related polytrauma is often related to stressful conditions caused by the working environment and modalities, rather than to the use of psychotropic substances such as alcohol, which can predispose to and increase the rate of injuries [22-26].

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From a pharmacological point of view, the approach to the polytrauma patient can be differentiated on a temporal basis into two different moments: pre-hospitalisation, an immediate pharmacological approach to the patient in order to stabilise his condition; post-hospitalisation, aimed mainly at treating and resolving the patient's pain condition. In these two moments, pharmacological therapy involves the administration of different drugs ranging from the most common crystalloids for volemic reintegration to the most recent molecules with antalgic activity.

Based on the above premises, the aim of this mini-review will be to analyse the main molecules with antalgic activity to be used to treat the polytrauma patient in both the acute and chronic phases. Furthermore, the therapeutic approach useful for the stabilisation and resuscitation of the polytrauma patient will be briefly described.

2. Patient stabilisations

When trauma is generated, such as when using mechanical or high-pressure tools, road accidents, or accidental falls at work [27], our body goes from a state of motion to a state of rest. This transition results in the absorption of energy by the body, which is transmitted to the patient and his anatomical structures, compromising the functionality of those that are less resistant. The organs that better withstand energy changes are those rich in elastic fibres, as opposed to inelastic ones such as the liver and spleen, which, being incompressible, break very easily. In cases where trauma is caused by penetrating objects, the extent of the damage is directly related to the mass of the object and the speed with which it penetrated inside the patient.

Furthermore, the trauma may be visible from the outside, or it may be internal, and in the latter case, it is crucial to properly assess the patient and subject them to imaging procedures. It must also be remembered that most polytraumatised individuals have two or more skeletal injuries that further impair their vital functions [28].

The main conditions affecting a polytrauma patient are respiratory failure, circulatory compromise (haemorrhage), infection, neurological damage and intense pain [29-32]. Precisely for these reasons, the choice of drugs to be administered in the immediate future must be based on their ability to re-establish a correct circulation, avoid bacterial infections, and ensure a prompt and rapid neurological recovery of the patient.

Few drugs are needed to treat the patient in this acute phase. The most commonly used ones include: volemic replenishment drugs (crystalloids and/or plasma expanders); vasoconstrictors (ephedrine); vagolytics (atropine); antimicrobials (ampicillin + sulbactam); fibrinolysis inhibitors (tranexamic acid); drugs with analgesic activity (ketorolac, morphine, fentanyl, sulfentanil, buprenorphine, lidocaine) [33-37].

There are also emergencies in which the subject is in a particular critical condition, or in such a state of agitation that a correct diagnosis or administration of the drugs previously analysed is not possible. In these cases, it is necessary to intervene with the administration of molecules with anaesthetic/sedative activity, including the most commonly used ones such as: propofol, etomidate and ketamine.

These molecules, thanks to the sedation of the patient, allow the doctor to conduct a careful and in-depth diagnosis of the patient that is useful for defining the most suitable therapeutic strategy for treating the patient.

3. Medications with antalgic activity

The pain generated by polytrauma injuries poses numerous challenges from a pharmacological point of view. Generally, pain management in the polytrauma patient requires a thorough understanding of the patient's history as well as a comprehensive examination and consideration of the trajectory of care. Multimodal options for treatment include drugs, regional anesthesia and non-pharmacological treatments. Furthermore, it is crucial to remember that rapid pain management is of paramount importance in order to prevent the development of chronic pain. In this regard, it is possible to identify two different stages for pain therapy in the polytrauma patient: a first stage in which the administration of analgesic drugs is directly related to the patient's condition and is subordinate to the monitoring of vital functions and diagnosis; a second stage in which the choice of drug should be made after a careful and thorough assessment of the type of pain, site, degree of interference on the patient's autonomy and quality of life [38-40].

In the first stage, analgesic drugs are used, the administration of which requires the intervention of an anesthetist; in the second stage, drugs are mainly used only after identifying the site of the pain and quantifying its extent.

4. Analgesics administered under the supervision of the anesthetist

Often, the polytraumatised person is in such a state of agitation that the doctor is unable to make a careful diagnosis. In such cases, sedative drugs are administered along with molecules with analgesic activity. Commonly used molecules include Ketamine, a parenteral anaesthetic agent with analgesic activity at sub-anaesthetic doses. It is a drug with antagonist activity on N-methyl-D-aspartate (NMDA) receptors with activity on opioid receptors [41-43]. This molecule, at a dose of 0.25-0.5 mg/kg i.v. is able to produce rapid and intense analgesia. Molecules such as the synthetic opiate fentanyl, which is about 75 times more potent than morphine, can be decisive if the patient does not present a state of intense agitation. In this case, it is desirable to combine analgesic therapy with drugs with anxiolytic or sedative activity as an adjuvant. Among these molecules we can mention midazolam, a centrally acting benzodiazepine capable of inducing drowsiness, muscle relaxation and short-term memory loss, and propofol useful both for sedation and for inducing deep anaesthesia [44-46]. As an alternative to these drugs, drugs capable of inducing loco-regional anaesthesia may be considered [47-49].

5. Analgesics administered chronically

The choice of analgesic drugs involves a thorough knowledge of the pharmacokinetic and pharmacodynamic properties of the molecules of interest.

These properties allow us to determine both the most suitable routes of administration and the possible occurrence of side effects. Furthermore, in the case of subjects taking one or more drugs, due to concomitant pathologies, knowledge of the properties of the analgesic drug allows us to avoid the possible occurrence of drug interactions.

Medications usually used for pain management include non-narcotic analgesics, non-steroidal anti-inflammatory drugs and paracetamol, or narcotics, opioids.

Non-steroidal anti-inflammatory drugs provide excellent pain relief due to their analgesic and anti-inflammatory action. These molecules inhibit cyclooxygenases (COX), enzymes necessary for the transformation of arachidonic acid into prostaglandin H (PGH₂) and subsequently into other endogenous regulators: prostaglandins D (PGD₂), E (PGE₂), F (PGF₂), prostacyclin and thromboxanes (TXA₂ and TXB₂) [50-51]. NSAIDs can be divided into different classes: salicylates (e.g. aspirin); acetic acid derivatives (e.g. diclofen and ketorolac); propionic acid derivatives (e.g. ibuprofen, ketoprofen); enolic acid derivatives (e.g. piroxicam and meloxicam); selective COX-2 inhibitors (coxibs) (e.g. celecoxib, etoricoxib); other NSAIDs (e.g. nimesulide). Among these molecules, Ketorolac seems to be endowed with good analgesic activity, such that the drug is useful in the treatment of post-operative pain [52,53].

Among molecules with analgesic activity, paracetamol remains one of the most widely used. The analgesic action of the drug seems to be linked to different mechanisms of action including, the inhibition of the centrally expressed COX-3 enzyme [54,55] and the activation of spinal 5-hydroxytryptamine type 3 (5HT₃) receptors that occurs through an interference of the drug with the serotonergic descending pathways of pain [56,57]. In addition, some research groups have recently demonstrated the presence of an active metabolite of paracetamol (the fatty acid amide N-arachidonoylphenolamine; AM404) capable of activating the vanilloid receptor subtype 1 (TRPV1) and inhibiting cellular uptake of anandamide. All this promotes an increase in endogenous cannabinoid (CB) levels, resulting in a potentiation of their analgesic action that occurs through spinal descending inhibition mediated by CB1 receptor activation [58-64].

Opioids are among the best known drugs with analgesic activity. Their biological effect is due to neuronal inhibition by blocking the release of excitatory neurotransmitters [65]. This effect is a consequence of the activation of a well-defined number of receptors, predominantly μ receptors (μ_1 and μ_2), involved in the modulation of pain perception.

Opioids are commonly classified according to their analgesic potency: weak opioids (codeine and tramadol) and strong opioids (buprenorphine, morphine, methadone, fentanyl, oxycodone, hydromorphone, tapentadol). The former have a limited potency and possess a threshold dose above which the pain-relieving efficacy does not improve but, on the contrary, the occurrence of adverse effects increases. The drugs belonging to this group are mainly found in pharmaceutical formulations for oral use, in combination with paracetamol (codeine-paracetamol; tramadol-paracetamol).

Strong opioids include tapentadol. This drug, in addition to acting on its own receptor sites, has the ability to inhibit the norepinephrine transporter [66], this makes it a particularly useful drug in the treatment of chronic pain such as neuropathic or mixed pain [67,68].

Should the above-mentioned molecules fail to resolve the problem, one can consider administering so-called adjuvant drugs. These are compounds that, although not classic painkillers, contribute in some way to the efficacy of the analgesic treatment.

These molecules include (i) tricyclic antidepressants (e.g., amitriptyline and nortriptyline), serotonin and norepinephrine re-uptake inhibitors (venlafaxine, duloxetine) and serotonin re-uptake inhibitors (fluoxetine); (ii) antiepileptics (e.g. carbamazepine, pregabalin, gabapentin); (iii) steroids (e.g., prednisone, dexamethasone).

6. Conclusions

The evaluation of the type of pain and the underlying pathogenetic mechanism, as well as the location of any irradiation, the qualitative and temporal characteristics, the degree of interference on the patient's autonomy and quality of life, are necessary to establish a suitable and careful pharmacological therapy aimed at resolving the pain sensation.

Today, thanks to the different therapeutic protocols, updated on the basis of the most recent scientific discoveries, the doctor has at his disposal all the tools useful in identifying the most suitable drug for the treatment of pain in all its forms. The possibility of choosing the drug in the shortest possible time is of great importance, especially in polytrauma patients in whom the timing between the identification of the best active ingredient and its administration is sometimes 'vital'.

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