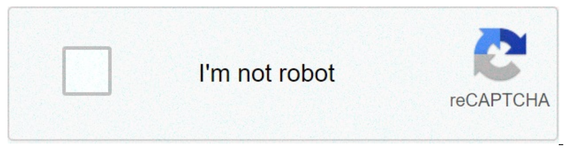

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The objective was to provide an authoritative consensus declaration that will considerably assisting in the selection and administration of an appropriate antidote. This scientific assessment is completed by detailed clinical information on routes of administration, contraindications, precautions and so on. The series will therefore collect a wealth of useful information that will be immense practical use for clinical toxycologists and all those involved in the treatment and management of poisoining. Scientific Editor T.J. Health Department of Meredith, London, United Kingdom D. Jacobsen Ulleval University Hospital, Oslo, Norway J.a. International Haines program on chemical safety, World Health Organization, Geneva, Switzerland J-C. Directorate of Health and Security Berger, Commission of the European Communities, Luxembourg EUR 14797 EN published by Cambridge University Press on behalf of the World Health Organization and the Commission of the European Communities Cambridge University presses the mention of specific companies or certain products of the producers It does not imply that they are approved or recommended by the World Health Organization preferably to others of a similar nature that are not mentioned. NÃ è The Commission of the European Communities nor no person acting on behalf of the Commission is responsible for the use that could be carried out by the information contained in this report. (c) World Organization of the Sanità, Geneva, 1993 and ECSC-EEC-EAC, Brussels-Luxembourg, 1993 published for the first time the publication of 1993 n. 14797 EN of the Commission of the European Communities, dissemination of the unity of scientific and technical knowledge, general management technologies and information and telecommunications industries, Luxembourg ISBN 0 521 45459 x Hardback content preface abbreviations 1. Introduction to the series 2. Naloxone 2.1. Introduction 2.2. Chemical name and formula 2.3. Physical-chemical properties 2.4. Pharmaceutical and synthesis formulation 2.5. Analytical methods 2.5.1. Quality control 2.5.2. Identification 2.5.3. Quantification of the antidote 2.5.4. Analysis of toxic agents 2.6. SHELF-LIFE 2.7. General properties 2.8. Animal studies 2.8.1. Pharmacodynamics 2.8.2. Pharmacokinetics 2.8.3. Toxicology 2.9. Voluntary studies 2.9.1. Pharmacokinetics 2.9.2. Pharmacodynamics 2.9.3. Effects of the high doses of Naloxone 2.10. 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References ANNEX I antidotes List APPENDIX II Principles for evaluation of antidotes APPENDIX III pro-forma for monographs on antidotes for specific WG toxic agents FOR VOLUME 1 EVALUATION OF ANTIDOTES Members Dr DN Bateman, Department of Clinical Pharmacology, University Newcastle, Newcastle-upon-Tyne, United Kingdom Prof. C. bismuth, hÃ 'pital Fernand Widal, Paris, France Dr RE Ferner, West Midlands poisons Unit, Dudley Road Hospital, Birmingham, UK (Joint rapporteur) Dr TJ Meredith, Department of Health, London, United Kingdom Dr H. Persson, Poison Information Center, Karolinska Sjukhuset, Stockholm, Sweden (Joint Chairman) Prof. L. Prescott, Scottish Poison Information Service, The Royal Infirmary, Edinburgh, Scotland (Chairman Joint) Dr. M.-L. Ruggerone, Niguarda Hospital, Poison Control Center, Milan, Italy Dr. H. Smet, Poison Control Center Belge, Brussels, Belgium Dr U. Taitelman, National Poisons Information Center, Rambam Medical Center, Haifa, Israel Dr. W. Temple, National Group Toxicology, Otago University Medical School, Dunedin, New Zealand (Joint rapporteur) Professor van Heijst ANP, Bosch en Duin, the Netherlands Dr G. Volans, poisons Unit, New Cross Hospital, London, United Kingdom Dr E. Wickstrom, National poison Center, Oslo, Norway Observer Dr G. Olibet, Poison Control Center, Milan, Italy Secretariat Dr Berger J.-C., Health and Safety Directorate, Commission of the European Community, Luxembourg Dr JA Haines, International Program on Chemical Safety, World Health Organization, Geneva, Switzerland Dr M. ten Ham, Pharmaceuticals Program, World Health Organization, Geneva, Switzerland Preface At a joint meeting of the World Federation of Associations of Clinical Toxicology poison control centers, the International Program on Chemical Safety (IPCS), and the Commission of the European Community (CEC), held at the headquarters of the World Organization of health in October 1985, the antidotes used in the evaluation treatment of poisoning has been identified as a priority area for international cooperation. In the course of 1986, the IPCS CEC have undertaken the preparatory phase of a joint project on this topic. For the purposes of antidote project it has been defined as a therapeutic substance used to counteract the toxic action (s) of a particular xenobiotic. Antidotes and partecipates © other agents used to prevent the absorption of poisons, in order to improve their elimination and treat their effects on the functions of the body, were listed and preliminarily classified according to the urgency of treatment and effective in practice. As for effectiveness, in practice, have been classified as: (1) those generally accepted as useful; (2) those widely used and considered promising but not yet universally accepted as useful and that require further research regarding their effectiveness and / or their indications for use; and (3) those of dubious utility. In addition, some antidotes or used for specific purposes agents were considered to correspond to the WHO essential drugs criteria (see Criteria for the selection of essential drugs, WHO Technical Report Series 722, Geneva, 1985). A methodology for the principles of antidotes evaluation and the agents used in the treatment of poisoning and a pro-forma for the preparation of monographs on antidotes for specific toxins have been prepared (respectively Annexes II and III). Monographs are in preparation, with the pro forma, for those antidotes and agents provisionally classified in Category 1 as far as the effectiveness in practice. For those classified in categories 2 and 3, where there are data or controversy regarding the effectiveness in Insufficient, it was agreed that a further study was necessary. As a result, many were selected for first examination and evaluation, among which were Naloxone as an antagonist for opioids, Flumazenil as an antagonist benzodiazepine and dantrolene for malignant hyperthermia. Maligna. Review and evaluation of these antidotes was launched at a joint meeting of the IPCS and the CEC, organized by the Northern Vilenity Unity and held at the Faculty of Medicine of the University of Newcastle-upon-Tyne, United Kingdom, 13- March 17, 1989. In preparation for this meeting, monographs have been drawn up, using the pro-forma, the Naloxone from Dr. DN Bateman, the Flumazenil from Dr. A. Brovard and Professor C. bismuth and the Dantrolene from Dr. H. Smet And Professor C. bismuth. The draft document on the Naloxone was evaluated by a work group consisting of Prof. L.F. PRESCOTT (President), Dr. W. Temple, Dr. D. Bateman, Dr. M. Ten Ham, Dr. Non.p. Van Heijst, Dr G.n. Volans and Dr. E. Wickstrom. Document projects on Flumazenil and Dantrolene were examined by a working group consisting of Dr. H. Persson (President), Dott R.e. Ferner (rapporteur), Dr. J.-C. Berger, Professor C. Bismuto, Dr. G. Olibet, Dr. M.-L. Ruggerone, Dr. H. Smet and Dr. U. Taitelman. Following the further editorial work meeting was undertaken by the authors, with the assistance of DRS R.E. Ferner, B. Britt (Department of Anesthesia, Faculty of Medicine, University of Toronto, Canada), and T. Fagerlund (Institute of Medical Genetics, University of Oslo, Norway) in the reformulation of the Dantrolene monograph. Text projects have been further revised by the Series editorial staff (Dr T.j. Meredith, Dr. Jacobsen, Dr. J.a. Haines and Dr. J.-C. Berger), which has also prepared an introduction to the series. This introduction summarizes the results of the preparatory phase and indicates the volumes currently provided for this series. The efforts of all those who have helped in the preparation and finalization of this volume are thank you. Abbreviations bzd benzodiazepine cat assisted computer tomography cns central nervous system gaba gamma-aminobutyrrico glc acid chromatography hiv human immunodeficiency virus hplc liquid high performance chromatography lsd acid lisergic dietilamide radioimmunological tlc chromatography thin layer gas-liquid uv ultraviolet 1. introduction to Antidote series play a vital role in the treatment of poisoned patients. Good support therapy, especially cardiac and respiratory systems, and the use of elimination techniques when indicated, make the majority of poisoned patients perform complete recovery. However, in some circumstances the use of antidotes can be life-saving, and in other circumstances the use of antidotes can reduce morbilities and medicals and other necessary resources in the treatment of a patient. In remote areas of hospital care, and in particular in countries where facilities for support therapy outside the hospital are often limited to development, the availability of some antidotes is even more essential for the success of the treatment of A poisoned patient. However, it remains controversy about clinical efficacy and indications for the use of many of the antidotes conventionally used in the treatment of poisoning. There is sometimes difficulty to get antidotes in an emergency situation, especially if the substance in question is not available as a pharmaceutical preparation. The need for an international evaluation of the clinical efficacy of antidotes and other substances used in the treatment of poisoning was recognized at a joint meeting of the World Federation of Associations of Clinical Centers of Toxicology and Polyners Control Centers, the International Program on Chemical Safety (IPCS) and the Commission of the European Communities (CEC), hold at the WHO headquarters, Geneva, October 6-9 1985. At the same time, the need to favor the widest availability of these effective antidotes has also been recognized. As a result, a Joint IPCS / CEC project was subsequently To face these problems. In a preparatory phase of the project, an antidote was defined for work purposes as a therapeutic substance used to counteract the toxic action (s) of a specific xenobiotic. A preliminary preliminary Of antidotes for revision, as well as other agents used to prevent the absorption of poisons, to improve their elimination and to treat their effects on body functions, has been established. For the purposes of the review process, the antidotes and other substances were classified according to the urgency with which treatment was thought with the antidote on current tests and the clinical efficacy (currently judged) of the antidote in practice. Those corresponding to the concept of an essential medication have been designated as such. Some have already been incorporated into the chemical list of essential drugs. Antidotes and similar substances for veterinary use were a use that (1988) of essential drugs. List of essential medication models (fifth list). Third report of the expert committee which. Who is the 770 Series Technical Report, Geneva World Health Organization. Also listed. A methodology on the principles for the assessment of antidotes and other agents used in the treatment of poisoning was developed and this was subsequently used as a framework for preparation of monographs on specific antidotes. The list of antidotes and other agents established as a result of the preparatory phase and the preliminary classification is provided in Appendix I. The principles for evaluation are detailed in Appendix II. In advance during the course of the preparatory phase, it became evident that antidotes availability differed from one country to another. The availability problems decreased in three interrelated categories, namely: * scientific, technical and economic aspects; * Regulatory and administrative requirements; * Geospacial considerations and time. The availability problems of antidotes used in the treatment of poisoning have therefore been examined by an IPCS / CEC work group, hosted by the Norwegian National Vinisons computer center and held in Oslo, 20-22 June 1988. The record of this meeting is given In ICS /88.44. In preparation for this meeting, a preliminary investigation of the selected poison control centers has been undertaken in order to more precisely identify the practical difficulties encountered in obtaining antidotes. The survey has shown that, in general, the centers of poisons in industrialized countries have had few problems in obtaining most antidotes, although the lack of adequate preparations / importers / producers together with administrative difficulties has hindered access to certain Antidotes. On the contrary, the centers in developing countries have recorded many problems in obtaining even those antidotes who are readily available elsewhere. A report was prepared by the IPCS / CEC work group that defines the problems associated with antidote availability and suggest modes in which antidote availability could be guaranteed for the treatment of poisoned individuals. In due course, it is understood that this relationship will be taken to the attention of all relevant national national authorities and import authorities, pharmaceutical manufacturers, pharmaceutical distributors and all poisons control centers. The guidelines for IPCS Polys control summarize the problems and issues of availability identified by the work groupb. B Who (in printing) - Guidelines for vehicle control, Part II, Section 6 Geneva, the aspects of the World Organization of the Assessment of Assessment of Antidotes The development and evaluation of substances to counteract the toxic actions of one Xenobiotico is mainly a task for the scientific community, in particular those working in experimental pharmacology, toxicology and clinical medicine. The effectiveness of a substance intended for use as an antidote must first be demonstrated in an appropriate animal model. Next step, demonstration of effectiveness in humans, it is often more difficult because there is rarely an opportunity for controlled clinical trials. Although a substance is demonstrated to be effective as an antidote, the potential intrinsic toxicity of the substance must be considered before its most widespread use, and, as well as All drugs should be considered the possibility of an adverse drug reaction. A clinical is more likely to be prepared to use a relatively "non-toxic" antidote (even one whose efficacy has yet to be established with certainty) of one with intrinsic toxicity. An antidote that is potentially toxic must be used only if it is therapeutically effective and the indication of use is clear. Although possible long-term negative effects and chronic toxicity needs to be taken into consideration, they are usually less importance than for an ordinary pharmaceutical agent because treatment with an antidote is rarely necessary more than once in a particular individual. A final consideration in the use of an antidote is that an increase in toxicity must not derive from the mobilization of the toxin from tissue stores or variations in tissue distribution. The concept of relative "effectiveness" of antidotes It is important that doctors employ antidotes in the treatment of poisoned patients recognize that "the clinical efficacy of antidotes varies considerably. On the one hand there are antidotes whose clinical effect is both rapid and dramatic. Examples would be Naloxone or Flumazenil, who act competitive antagonists as very specific to opioid receptors and benzodiazepines, respectively. On the other hand, there are antidotes who are able to counteract only some of the toxic effects of a particular compound; If the dose of the compound in question is sufficiently high so the patient risks dying despite the use of an antidote. Chelating agents provide good examples of antidotes that fall into this category of efficacy. However, chelating agents have an important role to play in the treatment of heavy metals poisoning, and many are recommended for this purpose in Volume V of this series. Some agents are vaguely defined antidotes even if they can have little or no real antidotal effect; They can still form precious appendices for treatment. Diazepam, used in the treatment of organophosphate poisoning (Volume IV), is an example. Temporary volume list IPCS / CEC antidotes series It is expected that the IPCS / CEC series of monographs on antidotes will cover all antidotes that are commonly used - or that have been proposed for use - in the treatment of intoxication. Once this objective has been achieved, the volumes are expected to be periodically updated, in order to meet the needs of healthcare professionals. At present, the volumes offered for this series include: Volume 2 Assessment of antidotes for poisoning from cyanide: oxygen * * sodium thiosulphate * hydroxicobalamina * Edited sodium * nitrite * sodium nitrite * 4 dimethylaminophenol * antidotes to metahemoglobin-forming agents (blue of Methylene, Toluidina Blue) * Analytical methods for cyanide alone and in combination with pawntoths Cianuro Volume 3 Assessment of antidotes for paracetamol poisoning * Overview * N-acetylcysteine * Methionina Volume 4 Assessment of antidotes for poisoning from organophosphates * Overview * Atropine * Diazepam * Obidoxy * Pralidoxime Volume 5 Evaluation of chelating agents for heavy metal poisoning * Overview * * Deferoxamine Blue Prussia * * Trientina Disodium soccer editato * * DTPA DMPS * * DMSA Dimercaprol * Penicillamina and N-acetyl penicillamin volume 6 antidotes for poisoning from Methanol and ethylene glycol. Volume 7 Antidotes for Amatoxin, Gyrometrine and Isoniazide Volume poisoning 8 Evaluation of the various pharmaceutical substances used for better elimination and prevention of absorption. Additional volumes are provided for: * General and sorbent antidotes * Antidotes based on international immunotoxicology Evaluation process experts required by the IPCS to draw up monographs of monographs on antidotes Specific agents, or on specific aspects related to their therapeutic use. Original bibliographic references must be used according to the established criteria for Environmental Health Criteria Documents. By What monographs are written according to agreed standards, a common format has been established according to the methodology relating to the principles for the evaluation of antidotes (Appendix II) and the guidelines for authors (Appendix III). The curators of the series examine the air currents to ensure that they comply with the standard format and are acceptable quality for para revision. For some volumes of a guest editor is also named. The IPCS sends the drafts of selected experts for the comment and for any additional information. A working group of authors and experts in the sector is then summoned by the IPCS and CEC. The task of this group is: (i) examine the literature whose monographs for its relevance, including the experience case experience; (Ii) identify any gaps in knowledge or scientific unknowns; (Iii) carry out an assessment of the clinical efficacy of the antidote for a particular poisoning or pathologies deriving from poisoning; (Iv) provide guidelines on treatment schemes, in various conditions of use of the antidote, including, where appropriate, the field and the use of basic health care, advisory on accompanying support therapy, and pay particular attention to pediatric doses , contraindications and special considerations. Following the work group Meeting further drafted may have to be undertaken by the original author in consultation with the series and the guest editors. A panoramic chapter that summarizes the problems and give the evaluation of a series of antidotes for specific types of poisoning cases is prepared by the publishers or experts invited. The IPCS and CEC can convene a further drafting meeting to finalize monographs for a particular volume and for the approval of the panoramic chapter. The volume is then developed by the editor which for the publication from the Cambridge University Press. 2. Naloxone 2.1 Introduction Naloxone is an opioid antagonist that acts to all three types of opioid receptors. It seems devoid of agonist activity (Martin, 1976). Naloxone is indicated in the treatment of opiate poisoning. Although Naloxone was also reported to be beneficial as an antidote in benzodiazepine (BZD) poisoning (Bell, 1975), other workers have not shown an effect in a double-blind study of induced diazepam sedation (Christensen & HÃ¼tel, 1979). However, Jordan (1980) demonstrated a certain reversal of Diazepam respiratory depression induced by Naloxone. There is therefore the need for further controlled studies, in particular in cases of poisoning. Naloxone is also sustained to have an effect on central depression induced nervous system (CNS), and in a study appeared to cause improvement in 20% of the cases treated (Jefferys et al., 1980). However, this data was not confirmed by other workers (Handal et al, 1983; .. Nutto et al, 1984). The possible beneficial effects of Naloxone in non-opiate poisoning probably reflect the involvement of endogenous opioids in the sedative action of some non-opioid drugs (McNicholas & Martin, 1984). 2.2 Name and chemical formula Naloxone 6-alllnoroximorphone 17-ALLIL-6-DEOSSI-7.8-Dihydro-14-hydroxy-6-bone-17-NORMORPHONE Empirical formula: C19 H21 NO4 Relative molecular mass: 327 CAS number: 465- 65-6 Business Names: Narcan, Nalone, Daffickies (Du Pont Pharmaceuticals) Naloxone is available for clinical use as salt hydrochloride, which can be anhydrous (CAS 357-08-4) or contain 2 hydration water molecules (CAS 51481 -60-8). The relative molecular mass of the free base is 327.37 and the anhydrous salt 363.84. Conversion Table: 1 g = 3.1 mmol 1 mmol = 327.4 mg 1 mg / ml = 3.1 mmol / l 1 mmol / l = 0.33 mg / ml The molecular structure of the Naloxone hydrochloride is shown below . 2.3 Physico-chemistry of the properties Naloxone hydrochloride has a fusion interval of Â ° C. It is soluble in water, diluted acids and strong alkalis, and is slightly soluble in alcohol, but practically insoluble in ether. Aqueous solutions are acide (pH 3-4.5) (United States Pharmacopeia, 1980) and a one Water solution is isotonic with serum (Hassan et al., 1985). A solution to 25% of Naloxone hydrochloride light wheel between -170 and -181. Naloxone crystals from ethyl acetate have a specific rotary power at 20 ° C ([alpha] D20; 9.3 g / l chloroform) of -194.5 Â ° ã, (Windholz, 1983). Naloxone has a Pka (20 Â, Â ° C) the values for nitrogen and phenolic groups h respectively 7.94 and 9.44, (Kaufman et al., 1975). When drying at 105 ° C, the anhydrous shape does not lose more than 0.5% and the hydrated shape no more than 11% of its weight. The solution injectable is constituted in water and must be protected from light. Naloxone can be diluted in saline with 0.9% or 5% dextrose and must therefore be used within 24 h. It must not be mixed in solutions containing metasulfite, metabisolphite or long chain or high related molecular weight anions, or in those with an alkaline pH. 2.4 pharmaceutical formulation was reported and three synthetic ways for the production of Naloxone (Hassan et al., 1985). Osimorefone is a starting point for two of the synthetic and 14-hydroxicodeinone processes for the third. hydrochloride Noroximorphone is a potential impurity from the production process. 2.5 Analytical methods 2.5.1 Quality control Naloxone hydrochloride can be dosed with gas chromatography with flame ionization detection (United States Pharmacopeia, 1980). 2.5.2 Identification about 150 mg of the unknown substance is dissolved in 25 ml of water and a few drops of ammonium hydroxide 6N are added. Three portions 5 ml of chloroform are used for extraction and extract is filtered. The filtered is collected, evaporated to dryness using a steam bath, and dried at 105 Â ° C for an hour. The infrared absorption spectrum of a 1-in-50 solution of the residue obtained in chloroform will have a maximum of wavelengths like those of a similar solution of Naloxone reference standards. Adding a drop of ferric chloride solution to 1 ml of a 1-in-100 solution of results Naloxone hydrochloride in clear violet color. 2.5.3 Quantification of the antidotus methods for Naloxone in biological fluids that employ gas-liquid chromatography (GLC) (Meffin and Smith, 1980), radioimmunological (RIA) (Berkowitz et al, 1975; .. Hahn et al, 1983) and High performance Liquid chromatography (HPLC) (Asals, 1983; Terry et al, 1984) have all been reported. The method includes GLC derivatization and the specific antibody for the AIR is not widely available. The reported HPLC methods appear sensitive and reproducible, and are probably the methods of choice. 2.5.4 Analysis of toxic agents in most cases in which Naloxone is used as an antidote, there is no way to measure the level of opioid poison. Current analysis techniques for many opiates are difficult, and ring suffers from lack of specifics in many cases. Some opiates, for example, morphine, seem to have active metabolites (Bodd et al., 1990). The most widespread method for opiaceo detection is urine. 2.6 Validity period The validity period of intravenous naloxone in temperate countries is 3 years and has a similar length in tropical countries. 2.7 General properties Naloxone is a specific opioid antagonist (Martin, 1976) and it is for this reason that it is used in the treatment of poisoning. There are reports that you can invert the central effects of ethanol and poisoning from BZD in humans. However, these are experimental uses that remain unhought, and any observed effects probably reflect the involvement of endogenous opioids in the unspecific depressive action of those agents (McNicholas & Martin, 1984). 2.8 Animal Studies 2.8.1 Pharmacodynamics Naloxone is a competitive antagonist of opiate receptors, and seems to be effective at all three types of receptors (Mu, Kappa and Sigma) (Martin, 1976). Does not produce In animal or human models of opiates tolerance and seems to be free of agonist activity in most laboratory laboratory test models 1967; McNicholas & Martin, 1984). It produces a parallel displacement in the effects of the in vitro dose-response of pure agonist opioids, such as morphine and partial agonists, such as Pentazocine (Smits & Takemori, 1970), Buprenorphine and Destropropoxuphene. Since the range and quantities of opioid receptors vary in different animal tissues, a range of Naloxone concentrations is needed to antagonize opioid effects into different test systems. The confusion arose that Naloxone is a pure antagonist. This is because some opioid receptors act as modulators and improve nocice stimuli. So, in some animal models Naloxone seems to possess agonistic effects, but this is in fact wrong (Sawynok et al., 1979). Naloxone was also observed in some experiments to antagonize the antinoc.time effects of some non-opiate drugs. Again it seems likely that it reflects an involvement of opioid receptors in the mechanism of action of these drugs (Sawynok et al., 1979). However, in a recent study in rats, Kotlinska & Langwinski (1990) has failed to find any evidence for the participation of the opioid system in the mediation of ethanol effects in rats. Naloxone was reported to decrease or has no influence on barbitourism-induced anesthesia. This paradox can be the result of the dose-response report of the effects of Naloxone, which at high doses can have a powerful effect (Sawynok et al., 1979). Naloxone has an activity like a Gabana antagonist and can therefore have a convulsed activity. However, this is likely to be at much higher concentrations than those encountered clinically (DingleDine et al., 1978), since in mice a dose of 100 mg / kg was required to produce convulsions. Naloxone has also been shown to have a number of biochemical effects in the rat, including the inhibition of lipolysis and a subsequent increase in circulating free tryptophan (Badawy et al., 1983). 2.8.2 Pharmacokinetics Naloxone seems to be readily absorbed after the oral administration, but it undergoes an extensive first passage hepatic metabolism, which translates into a very low bioavailability (Misra, 1978). Studies of intravenous naloxone pharmacokinetics were performed in a variety of animal species including rat, rabbit and dog. Many of these studies are based on Naloxone's immunoassay. The serum Naloxone concentration found 5 min after injection was similar (5 mg / kg) in the rat and the dog (Ngai et al., 1976; Peace et al., 1979). The half-life of the parent drug in the rat (30 minutes) was about the dog's half (71 min). Ngai et al. (1976) He also examined the brain: the serum report of the Naloxone and found it to vary in the rat between 2.7: 1 and 4.6: 1. The Naloxone administered intravenously acts quickly on the brain. The brain: the serum relationship was higher, however, when Naloxone was administered subcutaneously. These workers also studied, in a parallel group of animals, the distribution of morphine and noted that the brain: the serum ration was 1:10. The initial distribution of the Naloxone can represent the rapid onset of its reversal of the opact effects when it is administered intravenously. The main metabolite of the Naloxone is glucuronide. Naloxone-3-glucuronide was found, for example, in the rabbit (Fujimoto, 1969). A conjugate product of 6-hydroxity of Naloxone, N-ALLYL-14-HYDROXY-7.8-DIYRAMORMORFINA-3-Glucuronide has been identified in the Fujimoto chicken (1969); This conjugate has also been identified in the Rabbit of Weinstein et al. (1974) But only in small quantities. The relatively short action of the Naloxone seems to be from the facility with which he enters the brain after intravenous dosage and the next Rapid, elimination and consequent fall in the brain's Naloxone levels (Berkowitz, 1976). Naloxone's hydroxylate metabolites seem to possess narcotic antagonist activities, but their powers are much weaker than the parent compound. So it's unlikely to be meaningful in view of the little small Products (Fujimoto et al., 1975). The distribution of Naloxone was not found to be altered by a range of 25 times of the concentration of morphine in the rat (Fishman et al., 1975). 2.8.3 Acute toxicity studies with Naloxone were performed in mice, rats and dogs. The DL50 for intravenous administration was 150 mg / kg in mice, 109 mg / kg in rats and 80 mg / kg in dogs (social committee of 1976). For 24 h-rats the LD50 was 260 mg / kg when administered subcutaneously (Blumberg et al., 1966). The maximum toxic subcutaneous dose in the rats was of the order of 50 mg / kg (Blumberg et al., 1966). This dose has been tolerated for 24 days, while at 200 mg / kg caused tremors, convulsions and salivation. Daily doses of 0.2 mg / kg administered intravenously to dogs for 16 days and 5 mg / kg by subcutaneous in monkeys for 30 days did not cause toxicity. However, a subcutaneous dose of 20 mg / kg has determined lethargy and tremor in monkeys. No teratogenic effects were observed in mice, rats or rabbits when Naloxone by parenteral was given during the period of the organogenesis (social committee of 1976). There are no studies on mutagenicity have been published. 2.9 Volunteering Studies of Pharmacokinetic and Pharmacodynamics of Naloxone were conducted in volunteers. 2.9.1 Pharmacokinetics using a sage RIA, the pharmacokinetics of Naloxone were found to adapt to a model with two compartments, with a rapid distribution phase and a slow elimination phase, having a residence time of 64 min (NGAI et al ., 1976). More recent studies using HPLC to test Naloxone suggest that the apparent volume of distribution, half-life and clearance All differences show within groups of normal volunteers. So Aitkenhead et al. (1984) reported an apparent average volume of distribution to the stationary state of 3.65 l / kg (range 1.43-7.05 l / kg) and an average empticion of 151.2 min (interval 47.1- 313.2 min). Using a HPLC test, GoldFrank et al. (1986) They found a lower variability in patients (half-life 28-55 min). Naloxone's kinetics in newborns appear similar to those of adults (style et al., 1984). The oral administration of RadioMarky Naloxone a wide passage metabolism in normal subjects (Fishman et al., 1973). After intravenous administration, most (70%) of radioactivity was recovered in urine, most of which was conjugated as glucuronide. Furthermore, other metabolites were found in small quantities, ie the married of Normorphine glucuronide 7,8-Dihydro-14-hydroxy, and N-Allil-7.8-Dihydro-14-hydroxy-Normorphine (Weinstein et al. 1971). As a result of the elevated hepatic clearance of Naloxone and relatively weak agonist activity of its metabolites, it is unlikely that the dose adjustments may be necessary in cases of renal failure. Naloxone is only 54% of protein-bound in adult plasma (61.5% in fetal plasma), and this link is not dependent on the concentration in the range 9 ng / ml to 2.5 Ã‚Î¼g / ml (asals and Brown, 1984). So protein link interactions seem unlikely. The elimination of Naloxone can be altered in patients with hepatic disease, but no study seems to have been executed. 2.9.2 Pharmacodynamics studies were conducted on the duration of action and power of the Naloxone reversing respiratory depression induced by morphine (intravenous of 5 mg and 10 mg) in volunteers (Kaufman et al., 1981). The effect of Naloxone against this therapeutic dose of morphine reached a peak about 30 minutes, which was equatable with the probable cerebral concentration peak. It should be noted that the time of beginning effect and a naloxone peak differed. Naloxone's duration of action seemed to be about 1.5 h in this experimental. Johnstone (1974) examined the effects of an infusion of Naloxone in volunteers who had received 2 mg / kg intravenous by morphine and anesthetized state for 5 h. Intravenous Naloxone given to these volunteers at a speed of 40 Ã‚Â¼g / kg over a period of 10 h inverted the central depressive effects of morphine on respiratory respiratory (measured by CO2 reactivity) and higher functions (valued by a supervision test). No tachyphalaxis have been observed to the effects of Naloxone in this period (Johnstone et al., 1974). It was suggested that ethanol can exercise some of its effects through the endogenous opiate system, as illustrated by the study of Jeffffterys et al. (1980) and Jeffcoate et al. (1979) where Naloxone was found to antagonize some of the effects of ethanol. However, these results could not be confirmed by Handal et al. (1983) or swim et al. (1984). In the last study, the effect of Naloxone on ethanol-induced impairment of psychomotor performance was studied for the first time in two trials controlled by placebo, double-blind, in 17 healthy males volunteers. The main conclusion was that the Naloxone (intravenous doses of 0.4 more 2 mg) had no significant antagonization effects on the reduction of ethanol induced value (1.5 g / kg). However, a slight but significant effect on ethanol-induced nystagman was noted. A placebo-controlled double-blind study was subsequently conducted on alcoholized male allowed for acute ethanol intoxication (the average blood ethanol level was 2.9 g / l (64 mmol / l)). In this case, NÃ © Naloxone (intravenous doses of 0.4 more 2 mg; n = 11) nor saline solution (n = 7) had no effect, as judged by a clinical drunk test (swim et al., 1984). 2.9.3 Effects of high doses of Naloxone Naloxone were administered to healthy volunteers at dose levels of 0.3-4 mg / kg. These high dose levels have produced dysphasia and dose dependent dose. Furthermore, increases in blood pressure and respiratory rate were detected, together with increasing cortisol levels and growth hormone (Cohen et al., 1983). These results were used to support the hypothesis that endogenous opioids perform a normal regulatory physiological role, but obviously have potential therapeutic implications if Naloxone's great doses are used to treat poisoned patients. 2.10 Clinical studies - Naloxone clinical trials have been studied in clinical trials on both patients who received a therapeutic dose of an opacity (see section 2.9) and those who have been poisoned with opiates. Since the naloxone is a competitive antagonist, the dose required to reverse the clinical effects of a specific optello will depend on the dose of opium, its duration of action and its pharmacological properties, in particular if it has a partial agonist activity o Shows the selectivity to a type of subgroup for opioid receptors (Martin, 1976). 2.10.1 Effects in therapeutic use of opioids An alternative method to study the response to Naloxone was reported by Drummond et al. (1977). They studied patients who had been anesthetized and received the synthetic opact fentanyl. Naloxone produced an increase in the dose-dependent of the respiratory function (measured as a minute volume or respiratory frequency) with intravenous doses of 0.1, 0.2 and 0.4 mg. Hatano et al. (1975) reported an open study on 80 patients undergoing a variety of surgical procedures including cardiopulmonary bypass. The premedication included the petidine (Meridina) and the induction was reached with pentazzocine and Diazepam. The doses of Pentaskochine in males were 2 mg / kg and females 1.5 mg / kg, and those of Diazepam were 0.4 and 0.3 mg / kg respectively. The authors used a gradual increase in Naloxone (intravenous boli of 0.2 mg) to obtain the reversal of the opium effect of pentazocine at the end of the operating procedure and has detected a gradual inversion of opiating effects in their patients as it is The opacity dose was increased (the total average dose date was weight of 2.5 mg / kg). The duration of the Naloxone action in the emergence of the effects of morphine (5 or 10 mg, intramuscular) in patients recovering from surgery is relatively short (Longnecker et al., 1973). The authors suggested that the use of a combination of intravenous and intramuscular naloxone could be an appropriate regime in the post-operative situation; This has also been suggested suggested The treatment of acute overdoses in heroin addicts (see sections 2.12.2 and 2.13.2). 2.10.2 Effects in acute opaque warning Two important studies have demonstrated the effectiveness of Naloxone in advocating opposition poisoning. Evans et al. (1973) reported a study in which Naloxone (0.4-1,2 mg, intravenous) led to the recovery of consciousness within 1-2 minutes in nine patients with a matted swallow history. This was associated with improving the respiratory function in the six patients in which it could be measured with minute volume and respiratory rate. The opiats taken from these patients have been reported as a dipipanone (3), Pethidina (2), Diydtocodeine (2), pentasocine (1) and heroin (1). On the contrary, none of the 13 oversized patients at a variety of other depressions of the central nervous system showed an improvement after receiving a total intravenous dose of Naloxone from 1.2 mg. This quick and clear benefit of therapy has also been reported by Buchner et al. (1972), who studied the effects of Naloxone (from 0.005 to 0.01 mg / kg) in 10 children with methadone poisoning. Although they have not studied a control group, they confirmed the presence of methadones in biological liquids in some of their patients. These authors emphasize the importance of an adequate observation period for poisoned patients with long opiates and the need for repeated doses of Naloxone. Since the beginning of the effects of Naloxone is so rapid, it has proved relatively easy to confirm its effectiveness in opposition revenation to restore consciousness and improve breathing. Further extensive clinical tests in opaque poisoning have therefore not been performed. Henry & Volans (1984) stressed the importance of correctly classify drugs as opioids. A list of opioids is a useful reminder (Table 1) that agents such as loperamide and diphenoxylate can produce a significant systemic toxicity in overdose. A particular aspect of the use of Naloxone that requires consideration is that of the most appropriate dosing regime. The first human studies have confirmed that the duration of the Naloxone action was more short than it would have been expected by its plasma half life (Berkowitz et al., 1975). The long life of the action of some opiates is also a factor in the need to repeat the initial dose of Naloxone in poisoned patients (Gober et al., 1979). As an alternative to the repetitive dosage, several research workers suggested that intravenous loading doses followed by a constant state-of-the-drug infusion would be appropriate both in children (Gourlay & Coulthard, 1983; Tenenbein, 1984) and in adults (Bradberry & Raebel, 1981; GoldFrank et al., 1986) suffers from opiate poisoning. These schemes have appeared safe and effective in clinical use, but they do not obtain the need for tight monitoring during the treatment of respiratory function, conscious level and cardiovascular function. It is important to remember that some synthetic opioids, E.g., Desrtropropoxuphene, have been reported to produce toxic effects at high doses, which are not reversible from Naloxone (Barraclough and Lowe, 1982). These effects may be due to a direct action of Desrropropoxuphene on cardiac cell membranes. Table 1. alphabetical list of opioids drugsa Alletorphine Levorphanol Alphaprodine Loperamide Anileridine meptazinol Azidomorphine methadone Bezitramide Metofoline Morphine Buprenorphine Butorphanol Codeine Nalbuphine Norpipanone dextromoramide opiate oxycodone dextropropoxyphene diamorphine (heroin) dihydrocodeine Oxymorphone Difenoxin papaveretum Pentazocine Diphenoxylate Pethidine (meperidine) dipipanone Phenadoxone Ethoheptazine Phenazocine ethylmorphine phenoperidine etorphine Piminodine Pyritramide Hydrocodone TheBacon Hydromorphone Tilidate Ketobemidone Tramadol Levometadil Trimeperidina from Martindale (1982). Some of these drugs can be marketed as part of a combined preparation. 2.11 Clinical Studies - Report Relations For Cases Individual Relations of Published Cases confirmed the effectiveness for most of (Handal et al., 1983). In patients who are narcotic drug addicts, Naloxone can precipitate the characteristics of acute opium withdrawal. The doses up to 20 mg of Naloxone have been used in children without associated adverse effects (Handal et al., 1983). If patients with acute renal failure receive morphine for several days for various reasons (for example, for sedation while on a respirator), opioid toxicity can occur due to the accumulation of active-6-glucuronid metabolite morphine, which Rinata is excreted (Bodd et al., 1990). In such cases, opioid toxicity can last up to two weeks after the termination of morphine therapy, and the patient will need Naloxone's infusion to avoid respiratory depression. 2.11.1 Naloxone in clonidine Clonidan hydrochloride poisoning is an alpha-adrenergic central and peripheral antagonist still used in the treatment of hypertension. It has also been suggested for the treatment of opium withdrawal (Gold et al., 1980). The mechanism for this effect and for the declared effect of the Naloxone in some cases of clonidine poisoning (North et al., 1981; Kulig et al., 1982) is not clear, but the involvement of endogenous opioids has been suggested . However, the effect of Naloxone in clonidine poisoning cannot be confirmed by the et al banner. (1983). In a retrospective study of 47 consecutive children admitted due to clonidine poisoning (Wiley et al., 1990), only 3 out of 19 given Naloxone showed a temporary response. A child had an episode of severe hypertension associated with the Naloxone administration (0.1 mg / kg). Therefore, there is no clear documentation for the beneficial effect of Naloxone in clonidine revenation. 2.12 Summary of evaluation 2.12.1 Indications Naloxone was reported to significantly antagonize acute opioid toxicity and opioid effects within anesthesia. Its high therapeutic index and the possible beneficial effect in other poisoning allow diagnostic use in critically ill patients when opioid poisoning can be a differential diagnosis. 2.12.2 Routes and dose recommended in patients with defined opaque poisoning, Naloxone should be given by intravenous course until an improvement in the conscious level and breathing are not observed. This can lead to the administration of different milligrams of Naloxone if partial opioid agonists are administered, but 0.8-1.2 mg is usually sufficient in morphine or heroin poisoning. It is important to emphasize that a pharmacologically active dose of Naloxone in the opaque revenation can be higher than that normally recommended in anesthetic practice. In patients with suspected opiate poisoning, an intravenous injection up to 2 mg of Naloxone and the patient response monitored closely must be administered. If there is an improvement in the conscious level, the respiratory rate or cardiovascular parameters, additional Naloxone doses should be administered. The effect of the Naloxone should be visible within 1 to 2 minutes after the administration. Once a patient has regained consciousness, it is necessary to continue to monitor breathing and cardiovascular status at regular intervals. In the patient who took a great opiate overdose or an overdose of a long-lasting opacity, it may be necessary to repeat the dosage with the Naloxone. This can be conveniently established by establishing an intravenous infusion of Naloxone. A required dosing guide was suggested by Goldfrank et al. (1986). From studies of the pharmacokinetics of Naloxone in patients suffering from opaque poisoning, calculated that a time infusion of the two-thirds of the required dose initially to reverse the effects of the opium Naloxone levels about those present at 30 minutes after the initial bolus administration. Another approach to opioid warning that can sometimes be used usefully in drug addicts is to give 0.8-1.2 mg Naloxone intramuscolary before awakening the patient with an intravenous dose Naloxone of 0.4-0.8 mg (The highest doses are rarely necessary) (personal communication from D. Jacobsen, 1991). This It has been proven to be a useful practical approach, since many addicts © leave the hospital immediately after the effect of the intravenous dose. Since © naloxone has a duration of action shorter than all'optizzazione, patients are commonly riammessiti within one hour with miosis, coma and impaired respiration. This treatment approach, however, requires an adequate ventilatory support to the patient because of the short delay before it is given the intravenous dose. Naloxone may also be administered as a continuous intravenous infusion (approximately 0.5 mg / h in normal saline) to counter the effects of morphine metabolites in patients with acute renal failure (bodd et al., 1990). 2.12.3 More consequential therapy or support © Since many of these patients suffer from impaired breathing or respiratory arrest, it is extremely important to give oxygen and immediately support the ventilation of Naloxone waiting to be available for injection. If ventilation is under control and cyanosis is regressing, you should consider giving an intramuscular dose of naloxone prior to intravenous dose (see section 2.12.2). The pulmonary congestion or edema is occasionally seen in poisoning by opioids (heroin). It is usually transient and responds to supportive therapy (oxygen and ventilatory support) and naloxone. 2.12.4 Areas where there is insufficient information to make recommendations There are anecdotal riportazioni beneficial effect of naloxone in other types of acute poisoning, for example with ethanol, or clonidine. In the case of ethanol, these results were not confirmed in well-controlled studies on human volunteers, or in patients intoxicated (Nuotto et al., 1984). Even the claimed effect in poisoning by clonidine was challenged (Wiley et al., 1990). There are insufficient data to recommend the use of naloxone in poisonings than those involving opioids. 2.12.5 Proposals for further studies studies on the effect of naloxone in other acute poisoning should be encouraged. It may however be said that sufficient studies have been performed on the use of naloxone intoxication ethanol to rule out a possible beneficial effect. On the other hand, there is certainly a lack of controlled studies on the possible effect of naloxone in poisoning of clonidine. If the effects of naloxone are seen in patients assumed to have been poisoned by non-opioid, urine samples should be collected and analyzed by RIA for the presence of opioids. Otherwise, such "reports on the cases" are of little value. 2.12.6 Adverse Effects Naloxone has a high therapeutic index, but can result in signs and symptoms of withdrawal, eg., Seizures, in (heroin). Other adverse reactions, as described below, are very rarely seen. Cardiac arrhythmias, and in particular, the ventricular fibrillation caused by the rapid reversal of opioid effects with naloxone. These events can be a particular problem in patients who have recently undergone surgery or those accustomed to oppiatti (Cuss et al., 1984). These reactions may result from a release of sympathetic transmitters, since an increase in blood pressure and tachycardia have been demonstrated. Some cases of pulmonary edema after being reported the use of naloxone in anesthetic practice, but it is not clear in this situation that is the causative agent: the anesthetic, or the opioid antagonist (Partridge & Ward, 1986). 2.12.7 Restrictions on use The fear of the signs and symptoms of predictability should not inhibit the use of naloxone in those who need it medically. 2.13 The sheet of 2.13.1 model information using naloxone is indicated in management of opacia, is defined suspected. Opiative poisoning should be considered in comatose patients with compromised breathing. Miosis is an unreliable sign and is not required for a diagnosis of opioid poisoning. The high therapeutic Naloxone index allows its use when a diagnosis of opaque poisoning is uncertain. 2.13.2 Dosage and course since Naloxone is a competitive opiate opiaceo antagonist There can be no absolute dosage guidelines. Naloxone must be administered intravenously, in subsequent doses of 0.4 to 2.0 mg, until the desired answer is obtained. It should be noted that to reverse the partial effects agonists / antagonists, for example, pentazocine, buprenorphine and dentropossifene, much larger doses may be needed, and can be impossible to reverse the effects of buprenorphine. Failure to answer a total dose of 10 mg usually indicates: a) that poisoning is not due to opiates; b) that poisoning is due to a partial agonist / antagonist; or c) that cerebral hypoxic damage has occurred. It should be noted that DESTROPOSSFENE 'was reported to produce cardiac toxicity that is not reversible for the administration of Naloxone. The duration of action of the Naloxone is short; A careful monitoring is necessary and repeated doses can be necessary. The alternative is an intravenous infusion of Naloxone. The use of an hourly infusion of two-thirds of the Naloxone dose requested to revive the patient was reported to be effective, but the dosage must always be titled to the individual patient. Another alternative, which can be suitable for opiating drug addicts, is to give Naloxone (0.8-1.2 mg) intramuscularly first to wake up the patient with an intravenous dose of 0.4-0.8 mg. However, adequate ventilatory support must be given. The patient therefore has a "deposit" of antidote in case he / she moves away immediately after the initial treatment (like many drug addicts do). The administered dose for children must be reduced according to body weight (0,01 mg / kg initially). 2.13.3 Precautions / Naloxone Contraindications can induce symptoms and signs of acute opiating to drug addicts. If convulsions occur are better controlled with Diazepam (10-30 mg, intravenously). No dosage alteration seems necessary in the case of changes in renal function. The dose in children must be adjusted based on body weight to that used in adults. Adequate protection precautions must be taken by hospital staff, in the case of opiate drug addicts, bearing in mind the risk of infection from transmissible diseases by blood, such as hepatitis B and the human immunodeficiency virus (HIV). 2.13.4 Naloxone adverse effects has a very high therapeutic index and negative effects are seen rarely. Ventricular arrhythmias including ventricular fibrillation have been reported after a rapid inversion of severe opiating intoxication. This can be avoided if oxygen and adequate ventilatory support are also provided. The management of abstinence symptoms in drug addicts is discussed in section 2.13.3. 2.13.5 Use in pregnancy and breastfeeding Naloxone is not teratogenic in animals, but there are no data on the relevant man. Naloxone treatment does not seem to be a contraindication for breastfeeding, although opiates' poisoning may be of a contraindication. 2.13.6 Naloxone luggage for injection must be stored from light. His Shelf-Life is 3 years old. 2.14 References AITKENHEAD AR, Derbyshire Dr, Pinnock CA, Achola K, G & Smith (1984) Pharmacokinetics of Naloxone intravenously in healthy volunteers. Anesthesiology, 61: A381. Asals LA (1983) Determination of Naloxone in blood from high performance liquid chromatography. J Chromatogr, 278: 329-335. Asals La & Brown KF (1984) Naloxone binder protein in fetal adults and plasma. EUR J Clin Pharmacol, 27: 459-464. Badawy AA-R, Evans M, Punjani NF, and Morgan CJ (1983) Does Naloxone always act as an opiating antagonist? Life Ski, 33 (Suppl 1): 739-742. Banner W, Lund Me, and Clawson L (1983) Naloxone failure to reverse clonidine toxic effect. Am J Dis Child, 1170-1171. 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Flumazenil, an imidazobenzo-diazepine (AnexateTM), has shown to reverse the sedative, anti-convulsive, and the BDZS mystery effects. It has no convulsive action and its use has therefore been proposed to combat benzodiazepines in anesthetics, clinical toxicology and intensive care. 3.2 Name and chemical formula of antidote * Flumazenil Anexater (Roche Laboratories) * ETIL-8-Fluoro-5.6-Dihydrate-5-methyl-6-bone-4h-imidazo [1.5-a] [1,4] Benzo-Diazepina-3-Carboxylate * Empirical formula: C15H14O3N3F * Related molecular mass: 303.3 * therapeutic class: imidazo-benzodiazepine * CAS number: 755-81-4 78 * Conversion: 1 mmol = 303.3 mg 1 g = 3.3 mmol Ã‚Î¼mol / l = 3.3 x Ã‚1g / ml Ã‚1g / ml = 0.3 x Ã‚ÎMOL / L 3.3 Physical-chemical properties of FLumazenyl physical-chemical properties are shown in Table 1. Flumazenil remains stable when exposed to light and when preserved for 2 years at 35 Â ° C. The weight loss for drying is up to 1%. 3.4 Pharmaceutical formulation and synthesis No information on synthesis and production paths are available. Flumazenil is supplied for parenteral administration in vials containing 5 or 10 ml of aqueous solution (0.1 mg / ml). It is available for oral administration as tablets of 10, 20 or 30 mg. Property Table 1. Physico-chemical Flumazenila Melting point 198-202 Â ° C Solubility in water

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