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Naloxone : Opening Up New Vistas

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ABSTRACT

The general awareness about poisoning is relatively low among Indian physicians owing to various reasons. The situation is beginning to improve with the advent of poison information centres being established in major hospitals, and more emphasis being advised by the Medical Council of India in the undergraduate medical curriculum on Toxicology. Several antidotes with proven efficacy against common poisons have recently been introduced into India, one of which is naloxone, the antidote of choice for opiates. Considering its value in this regard as well as its other applications, this paper analyses its tremendous potential in the clinical scenario.

INTRODUCTION

Antidotal therapy constitutes an important aspect of the management of poisoning. Unfortunately, genuine antidotes exists only for a small proportion of poisons, and even among these many are not available in India[1]. The situation is however beginning to improve lately with the introduction of antidotes such as D-penicillamine, desferrioxamine, dimercaprol, and pralidoxime. A new entrant is naloxone which has now effectively replaced nalorphine in the management of opiate and opioid overdose. The latter has therefore been withdrawn from the market. But a general (though limited) survey conducted in a random fashion among private practitioners as well as physicians working in some of the hospitals of South India demonstrated a very low awareness about the local availability of antidotes in general, and naloxone in particular (Table No. 1). Nearly 25% of the doctors queried admitted that they were unsure as to whether naloxone had been introduced into India, and 35% were under the impression that nalorphine was still available.

Table 1. Awareness among 100 randomly selected physicians about the availability of opiate antagonists*

Nature of information	Number of positive responses	Percentage
No opiate antagonist available	8	11.8
Only nalorphine available	9	13.2
Only naloxone available	20	24.4
Both nalorphine and naloxone available	15	22.1
Not sure as to whether either is available	16	23.5
* Only 68 responded.		

This ignorance is partly because many general physicians do not undertake the management of poisoning cases and refer these cases instead to intensive care units where "specialists" are available (though it is a sad fact that the latter are themselves mostly self taught as far as toxicology is concerned). The irony is complete when one considers the fact that in India, forensic specialists who do not treat poisoning cases at all, teach medical students about the management of poisoning.

It is imperative that more awareness is created among medical professionals about the availability of different kinds of antidote and thus encourage their use in specific cases of poisoning. This aspect is all the more important with regard to antidotes such as naloxone which demonstrate wide applications, and therefore can be used in a larger variety of cases. Even with reference to the main application of naloxone, i.e., treatment of opiate and opioid overdose, recent toxicological surveys have demonstrated that such cases constitute a significant proportion of seriously poisoned patients in whom the mortality can touch forty per cent[2].

DISCUSSION

Structurally, naloxone is N-allylnoroxymorphone, and is available in India as Narcotan injection (1 ml ampoules of 400 mcg/ml, and 2 ampoules of 20 mcg/ml). Today, naloxone is the antidote of choice for the treatment of opiate overdose. Previously, two other antidotes were used: nalorphine and levallorphan tartrate. But they induce respiratory depression and posses undesirable psychotomimetic side effects[3].Table 2 displays the advantages of naloxone over these obsolete antidotes.

Table 2. Comparative analysis of antidotes in opiate overdose

Property/Feature	Naloxone	Nalorphine, Levallorphan
1. Nature of narcotic antagonism	Specific and pure	Mixed agonistic and antagonistic effects
2. Respiratory depression	Nil	Present
3. Effect on the pupils	Nil	Miosis
4. Psychotomimetic side effects	Nil	Present
5. Minimum effective dose	Less	More
6. Efficacy against pentazocine	Effective	Ineffective
7. Safety in polydrug ingestion	Safe	Unsafe

Naloxone is the most effective opiate antagonist because it successfully competes for position at all the three recognised opioid receptor sites (mu, kappa, and sigma). Therefore it can reverse not only the respiratory depressant, analgesic, and euphoric effects of opiates, but also the dysphoric, delusional, and hallucinatory properties of synthetic opioids[4]. The usual dose is 400 mcg (0.4 mg) to 2 mg as a single dose, preferably administrered intravenously. Subsequently it may be repeated at 2 to 3 minute intervals as needed. Alternatively, naloxone can be given as a continuous i.v.infusion at a rate of 0.4 to 4.0 mg/hr depending on the response.

Mofenson and Caracio have devised a step-wise schedule for infusion therapy with naloxone after the bolus dosing has been determined[6].

Step 1: Determine maintenance fluid requirements for 24 hours.

Step 2: To determine the amount of naloxone (in mg) to be added to the maintenance fluid for a 24 hour period, take the amount required for the initial response, and then multiply successively by 2/3 and 24 (hours)

Step 3 : To determine the desired rate of naloxone infusion (in ml/hr), take the maintenance fluid (step 1), and divide by 24 (hours).

This method reduces the risk of possible fluid overload, especially in children, and the potential for pulmonary oedema. If intravenous access is difficult, naloxone can be given intramuscularly or subcutaneously at intervals. Some authorities suggest sublingual injection, where-in 0.4 mg of the drug is injected with a 22 gauge needle into the mid-ventral surface of the tongue, after aspiration with no blood return.[7] However, there is a danger of intra oral bleeding and airway compromise apart from the risk of being bitten by the patient while the injection is being administered![8]

For infants and children (upto 5 yrs or 20 kg body weight), the currently recommended dose of naloxone is 0.1mg/kg. Older or heavier children can be given 2.0 mg. These doses may be repeated as needed. Previously, a much lower dose was recommended (0.001 mg/kg) which is ironically even now mentioned on the product label itself. The new high-dose regime does not pose any enhanced risk for adverse effects.[9]

The major side effects of naloxone include hypotension, cardiac arrhythmias, convulsions, pulmonary oedema, and rarely cardiac arrest.

Other applications of naloxone

Naloxone is one of the ingredients of the "coma cocktail" widely recommended today for administration to all poisoned comatose patients in whom the exact identity of the poison is uncertain, the other two being dextrose and thiamine.[10]

There have been encouraging reports about the role of naloxone in reversing the coma associated with alcohol intoxication.[11] The exact mechanism is unclear.[12] In one case, naloxone along with activated charcoal helped to reverse the unconsciousness caused by valproic acid overdose.[13]

Several reports have appeared in the medical literature about the utility of naloxone in raising the blood pressure of patients with hypovolemic septic shock.[14,15] But this has to be weighed against the results of a prospective, randomised, double-blind, placebo controlled study which showed that 0.4 to 1.2 mg naloxone i.v., is no better than placebo in the amelioration of hypotension in septic shock.[16] Further studies are therefore necessary before recommending naloxone for the treatment of shock.

An anecdotal report suggests that i.v., naloxone can help in reversing the hypotension associated with captopril overdose.[17]

Naloxone also appears to be beneficial in spinal injury where it is said to improve neurologic recovery.[18] There are also indications that it is helpful in schizophrenia when combined with neuroleptic medication.[19]

From the foregoing, it is evident that naloxone has the potential to develop into a wonder drug with far reaching ramifications apart from its well established role as the antidote of choice for opiate and opioid overdose.

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