A Comprehensive Review of Naloxone for the Emergency Physician

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Naloxone, an opioid antagonist, is the most frequently prescribed specific antidote for human poisonings. According to the 1992 Annual Report of the American Association of Poison Control Centers,[1] which underestimates poisonings because of phone data collection, naloxone was used in 7,045 cases. This represents 1.5% of all poisonings seen at health care facilities.

In addition, naloxone is being tested and used for septic and hemorrhagic shock, for neonatal asphyxia, for stroke and acute spinal cord injury, and for reversing the depressant effects of several intoxicants other than opioids. Pediatricians, emergency physicians, and others caring for children should be aware of the potential uses of this medication.

PHARMACOLOGY

Mechanism of Action

Naloxone is the N-allyl derivative of oxymorphone. Like the other opioid antagonists, it acts by competitively binding at opiate receptors. However, unlike nalorphine and levallorphan, naloxone has little or no agonist activity and does not cause apnea.[2,3] Therefore, it can be used safely to treat patients with respiratory depression. Naloxone binds most strongly to the mu receptor but displays antagonistic activity at kappa and sigma receptors as well.[3,4]

Pharmacokinetics

Naloxone is reliably absorbed (75%) through the gastrointestinal tract but undergoes extensive first-pass metabolism, rendering this route ineffective unless large doses are used.[5,6] Therefore, it is usually administered parenterally.

Naloxone is effectively absorbed via intravenous, intramuscular, and subcutaneous routes.[7,8] It is also absorbed when administered endotracheally.[9,10]

Naloxone is highly lipophilic so that distribution to the brain is rapid. The distribution-phase serum half-life is 4.7 minutes after an intravenous dose.[11] Clinical effects are seen within 2 minutes when administered intravenously and are only slightly delayed when administered intramuscularly or subcutaneously. Naloxone crosses the placenta rapidly but fetal serum levels are lower than maternal levels.[12]

After absorption and distribution, naloxone is slowly released from the tissues, with a β-phase elimination half-life in adults of 64 minutes (range, 30 to 81 minutes).[11] Fishman et al[5] determined a serum half-life of 90 minutes in two subjects and found that heroin withdrawal shortened the serum half-life in an individual from 100 to 70 minutes. This is in accordance with the work of Garrett et al, who showed that the simultaneous administration of morphine to dogs caused decreased naloxone clearance.[13]

Studies in neonates have yielded conflicting results. In a sample of 10 premature infants with a mean weight of 1,328 grams, the serum half-life was 70.8 ± 35.6 minutes.[14] In contrast, the mean plasma half-life in a study of healthy neonates was 3.1 ± 0.5 hours. Peak levels were not achieved for 40 minutes in many of these subjects, so concern has been raised that administration via the umbilical vein may have resulted in infusion into the hepatic system (and measurement of a metabolite rather than naloxone itself) or a delay in reaching the systemic circulation.[15]

The primary mechanism of metabolism of naloxone is glucuronide conjugation in the liver, followed by urinary excretion.[16] To a lesser extent there is N-dealkylation and reduction of the 6-keto group.[17] Reduction of the 6-keto group in humans causes formation of the 6-β-naloxol metabolite, which has antagonist activity. Other species form both α- and β-epimers; the 6-α-naloxol metabolite displays agonist activity.[18,19]

Ngai et al[11] studied the pharmacokinetics of morphine and naloxone in rats and humans. Serum half-lives were similar for morphine and naloxone in both rats and humans, but despite falling serum levels, morphine persisted in the rat brain at higher levels than naloxone. Wahlstrom et al[20] showed that human brain tissue metabolizes naloxone more rapidly than morphine; moreover, morphine produced pharmacologically potent metabolites. These studies may explain the shorter duration of action of naloxone, although other theories have been proposed, including effects of sodium shifts at receptor sites[3,21] and differential plasma protein binding.[8] Other possible explanations, such as differing affinities for receptors or different rates of systemic elimination, have been largely dismissed.[8]

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Duration of Action

Early pharmacologic studies by Jasinski et al[22] showed that pupillary constriction and subjective scores of morphine's effects were lessened for at least 9 hours after high doses (15 mg) of subcutaneous naloxone when used to pretreat morphine. In contrast, Evans et al[23] showed a reversal of morphine effects on pupil size, pain threshold, ventilatory response to hypercarbic challenge, and subjective feelings of alertness for only 45 minutes after intravenous naloxone 0.4 mg in adults.

Longnecker et al[24] studied naloxone's effects in postoperative patients who had received morphine. Intravenous naloxone 0.005 mg/kg reversed morphine's effects for a mean duration of 79 minutes. A higher dose of 0.01 mg/kg was effective for 99 minutes. A combination of intravenous (IV) naloxone 0.005 mg/kg and intramuscular naloxone 0.01 mg/kg produced satisfactory reversal for at least 6 hours.

In case reports using naloxone in children, repeat doses have been required as soon as 30 minutes or as long as 5.5 hours after the initial dose.[25-27]

As with all drugs metabolized predominantly by the liver, there is individual variation in the metabolism and, therefore, the duration of clinical effect of naloxone. In addition, the duration of action depends on the dose and route of administration. In general, clinical efficacy for opioid antagonism lasts for 45 to 70 minutes,[8] although some investigators have reported clinical effects persisting for longer. The need to repeat doses to antagonize opioid medications will depend on the duration of effect for any given narcotic based on drug, dose, and route of administration. Careful observation of the patient for recurrence of opioid effects is warranted whenever naloxone is administered.

Because it is often necessary to administer naloxone repeatedly in patients with narcotic intoxication, the use of a continuous intravenous infusion has been investigated. Continuous infusion is more convenient than administering repeated boluses and provides sustained tissue levels of naloxone, thus preventing relapse of narcotic effects.

Johnstone et al[28] studied the effects of continuous infusion of naloxone 0.004 mg/kg/h in postoperative adults who had received morphine. Patients responded well to this regimen with gradual awakening and no complaints of a sudden return of pain.

Lewis et al[29] used a continuous infusion of naloxone at 0.027 mg/kg/h to reverse respiratory and central nervous system depression caused by codeine in a 31-month-old girl. They recommended continuous infusion to prevent relapse if: patients failed to respond to the formerly recommended initial dose of 0.01 mg/kg but responded to 0.1 mg/kg; patients showed recurrent respiratory or central nervous system depression after initial improvement with bolus therapy; or patients ingested a long-acting or poorly antagonized agent such as methadone. Their first recommendation has been superseded by the realization that 0.01 mg/kg is often an inadequate dose; thus, failure to respond to this dose may not predict the need for a continuous infusion.

Others investigators have treated infants, children, and adolescents with naloxone infusions ranging from 0.0025 to 0.16 mg/kg/h for as long as 5 days without adverse effects. Investigators have been unable to determine a relationship between the dose of naloxone required and the age of the patient or the agent ingested.

Recommendations for Dosing

Specific pharmacokinetic studies have not been performed in children except neonates. From case reports, it would seem that the duration of action is approximately the same in children as adults.

As Tenenbein[32] pointed out, dosing of naloxone is by necessity empiric. Most of the factors that would influence the correct dose of naloxone, eg, amount of opioid ingested, its central nervous system penetration, and its affinity for particular receptors, are unknown in the clinical setting. He agreed with the recommendations of Moore et al[34] of 0.01 mg/kg dose initially, repeating a dose of 0.1 mg/kg if the lower dose fails. Tenenbein and Moore based these recommendations on experience with patients who required higher doses and on the safety of naloxone in high doses.[22,35-38]

Because of naloxone's outstanding record of safety and concern about inadequate dosing after narcotic intoxication, the most recent recommendations are higher. The currently recommended initial dose of naloxone for children (including neonates) is 0.1 mg/kg. Children older than 5 years of age or weighing more than 20 kg should receive the adult dose of 2 mg.[39] Higher doses may be required for poorly antagonized opioids (eg, propoxyphene or methadone).

The most important point for the clinician to remember is the brief duration of action of naloxone when compared with that of most opioids. (Fentanyl and its derivatives may be exceptions.) Therefore, repeat doses of naloxone may be required, and the patient must be observed carefully in the emergency department. The use of a continuous infusion should be considered when repeat doses are required.

Lewis et al[29] recommended a starting dose for continuous infusion of 0.4 mg/hr regardless of patient weight, with titration to clinical response. Tenenbein[32] recommended starting an infusion at a rate to deliver the same quantity of naloxone per hour, to which the patient responded as a bolus. After stabilization, the infusion can then be weaned as tolerated or increased as needed. We recommend the method used at Bellevue Hospital (New York, NY). Based on human pharmacokinetic data and a computer model, physicians there repeat half of the initial successful bolus dose at 15 minutes while infusing two thirds of the bolus dose per hour.[40] Decreases in infusion rates should be gradual to prevent relapse.

SAFETY

Experiments in humans have shown naloxone to be safe, albeit not without occasional minor side effects. Jasinski et al[22] administered doses of naloxone as high as 24 mg/70 kg to adults. The only side effects were a subjective feeling of sleepiness in some subjects. Cohen et al[41] administered naloxone in doses up to 4 mg/kg to six volunteers. Alterations in mood and cognition occurred. Two volunteers withdrew from the study because of mental discomfort, including feelings of anger and frustration. In a Phase I trial of naloxone for the treatment of acute spinal cord trauma, Flamm et al[42] administered doses as high as 5.4 mg/kg loading and 4 mg/kg/h infusion for 23 hours to patients who were not receiving

pain during naloxone treatment in 4 of 29 patients. One patient had pain severe enough to warrant discontinuation of naloxone. Estilo and Cottrel[43] studied naloxone's effects in anesthetized patients not receiving narcotics. They found that naloxone had no effect on mean arterial pressure, heart rate, or plasma norepinephrine, epinephrine, or dopamine levels. Finally, other patients have received very large doses of naloxone to reverse opioid-induced narcosis, but none suffered adverse effects.[32,36,44]

In contrast, there have been several case reports of life-threatening adverse events in adults receiving naloxone after general anesthesia. These have included: hypertension and atrial tachycardia,[45] ventricular tachycardia and fibrillation,[46] left ventricular failure and pulmonary edema,[47] severe hypertension with atrial premature contractions,[48] sudden death,[49] and hypertension with rebleeding of a ruptured cerebral aneurysm.[50] Except for two healthy adult females, these patients had underlying cardiac or pulmonary disease, and all adverse events occurred when naloxone was used to reverse narcotic depression postoperatively. Multiple medications had been administered so it is difficult to prove a cause-and-effect relationship. Interestingly, because of two patients who developed ventricular fibrillation, Michaelis et al[46] were prompted to administer morphine and naloxone to dogs. Naloxone did not increase ventricular irritability.

Also worrisome are the case reports by Prough et al[51] of acute pulmonary edema in two postoperative adolescents after naloxone administration. Naloxone doses were conservative (0.1 mg and 0.5 mg, respectively), and intraoperative fluids were not excessive. It has been postulated that postoperative patients given naloxone may experience a sudden return of severe pain, causing a massive outpouring of adrenal catecholamines.

We found two published cases of adverse effects in unanesthetized adults. Both patients had underlying pulmonary or cardiac disease.[52,53]

In summary, naloxone has been administered millions of times without major side effects and has an impressive safety record. The case reports cited previously on anesthetized adults do not necessarily prove a causal relationship. If naloxone was the cause, these adverse outcomes may represent idiosyncratic reactions. There have been no reports of adverse effects in children when naloxone was used to reverse narcosis. However, because of the case reports in adults, one should be cautious when administering naloxone postoperatively to children with chronic cardiac or pulmonary disease.

CLINICAL EFFICACY

Overdoses

Narcotics

Several studies in infants have shown the efficacy of naloxone in reversing narcotic effects. Evans et al[54] randomized neonates of pethidine-treated mothers to receive either naloxone 0.04 mg IV or no treatment. Naloxone improved alveolar P_{CO_2} for at least 30 minutes. Wiener et al[55] also reported improved alveolar ventilation with naloxone in newborns whose mothers had received pethidine. Gerhardt et al[56] studied 24 newborns whose mothers had been treated with meperidine. Naloxone 0.01 mg/kg intramuscularly caused normalization of CO_2 response curves at 4% CO_2 compared with placebo controls. Finally, Fischer and Cook[57] administered 0.005 mg/kg naloxone to six infants recovering from general anesthesia with narcotics. Mean minute ventilation increased by 50% over control infants and was chiefly caused by an increase in tidal volume.

Other investigators have reported naloxone's efficacy in older patients. The New York City Poison Control Center cited early experience for methadone poisoning in children and adults and noted relapses in some patients who were treated and released.[58] They suggested observation for at least 48 hours, with repeated doses of naloxone as needed. The Regional Poison Center of Edinburgh reported dramatically increased levels of consciousness, minute ventilation, and blood pressures in nine patients with narcotic overdose but no effects in patients who took barbiturates or sedative/hypnotics.[59] Kaufman et al[60] reported a series of 49 adolescents with heroin intoxication. Intravenous naloxone, nalorphine, and levallorphan were effective in improving mental status, but repeat doses were required in most cases. Several case reports have shown naloxone to be effective for diphenoxylate (Lomotil, G.D. Searle & Co., Chicago, IL) poisoning,[36,61,62] and other reports have shown successful treatment of infants and children with methadone, dextromethorphan, and propoxyphene toxicity.[26,63-65]

Clonidine

Clonidine is an antihypertensive agent that acts centrally by stimulating alpha receptors. In normal doses, clonidine can block pain,[66,67] cause cross-tolerance for morphine,[66] and reverse the symptoms of opiate withdrawal.[67,68] In an overdose, clonidine resembles the opioids; hypothermia, coma, miosis, respiratory depression, bradycardia, and hypotension are characteristic. It has been postulated that clonidine interacts with opiate receptors, probably via intermediate pathways. Consequently, emergency physicians have used naloxone to treat coma, apnea, and hypotension associated with clonidine intoxication. Naloxone's effects seem to be mediated centrally.[69,70] Farsang and Kunos[69] showed that naloxone does not compete directly with clonidine for rat brain binding sites and that an intermediate pathway is therefore involved, presumably an endogenous opioid pathway.

The use of naloxone to reverse coma caused by clonidine intoxication has met with mixed results. Bamshad and Weserman[71] found naloxone beneficial in 5 of 10 pediatric cases of clonidine ingestion. Other case reports in young children suggest that clonidine may help to reverse coma and apnea caused by clonidine.[72,73] In contrast, none of Banner's five pediatric cases responded to naloxone in doses as high as 0.1 mg/kg.[74] Similarly, a chart review of 47 consecutive children with clonidine ingestion showed a definite response to naloxone in only 3 of 19 patients and a questionable response in another 4 patients. Naloxone may have been administered to a sicker subgroup of patients, because intubation and admission to the intensive care unit occurred more frequently in the naloxone group.[75] Undoubtedly, naloxone has been administered many times without success;

the frequency of this occurrence is impossible to define and is probably underrepresented in the literature.

The data regarding the treatment of clonidine-induced hypotension is likewise contradictory. Using small doses of clonidine in six adult volunteers with essential hypertension, a naloxone infusion of 0.006 mg/kg/h did not alter the therapeutic effects of clonidine on supine or standing blood pressure or heart rate.[76] In contrast, Farsang et al[77,78] identified a subgroup of patients for whom 0.4 mg IV naloxone reversed the therapeutic hypotensive effects of clonidine. These patients had higher baseline sympathetic tone (as measured by cardiac output), stroke index, epinephrine, and plasma renin activity. Similarly, spontaneously hypertensive rats responded to naloxone by reversal of clonidine-induced hypotension and bradycardia, whereas normal rats did not.[79]

North et al[80] found naloxone beneficial in treating hypotension and apnea in a patient with clonidine overdose. Since their report, several investigators have reported the efficacy of naloxone in reversing hypotension and/or bradycardia in individual cases of clonidine intoxication.[72,81,82]

One must use caution when administering naloxone to patients with clonidine intoxication. Gremse et al[83] reported three cases of toddlers who were treated with naloxone for clonidine overdose. All three developed hypertension; one had prolonged, severe hypertension requiring treatment with phentolamine. The investigators postulated that naloxone inhibited the central effects of clonidine, allowing its peripheral effects to predominate. While administering naloxone to adult volunteers with essential hypertension, Levin et al[84] found one patient in whom naloxone (8 mg IV) alone caused severe hypertension and in whom naloxone reversed the hypotensive effects of clonidine.

Keeping the aforementioned caution in mind, we agree with the recommendations of Kulig and Rumack,[85] who argue for trying naloxone in patients with drug-induced coma, regardless of the suspected agent, because of the potential benefit and the minimal risk. Because of conflicting results with naloxone in clonidine intoxication, a prospective study is needed. Even if such studies find naloxone effective, it is unlikely that naloxone will dramatically alter the ultimate outcome of pediatric clonidine ingestions because mortality is rare. However, the use of naloxone infusions might prevent morbidity associated with the need for artificial ventilation and intensive monitoring.

Benzodiazepines

One case report of a child and two reports of adults suggest that naloxone may be useful in some patients with overdose of benzodiazepines.[86-88] In addition, a double-blind crossover trial showed that 15 mg IV naloxone could reverse diazepam-induced depression of ventilatory response to hypercapnia.[89] Similarly, Gumulka et al[90] showed that 5 mg/kg naloxone partially antagonized the sedation and the decrease in cerebellar cyclic guanosine monophosphate produced by diazepam in mice. However, in contrast, Christensen and Huttel[91] were unable to show any difference between naloxone (0.4 mg IV) and saline in patients who had received diazepam sedation for endoscopy. Naloxone is certainly not universally efficacious in treating benzodiazepine intoxication, and any potential use in this poisoning has been supplanted by the availability of flumazenil.

Ethanol

Ethanol has complex mechanisms of action in the central nervous system. Davis and Walsh[92] postulated an interaction between ethanol metabolites and dopamine to form isoquinolines, which are structurally similar to opioids and may be intermediates in the biosynthesis of opioid alkaloids. The investigators speculated that this opioid pathway may play a role in ethanol addiction. Although many investigators have criticized this theory, it stimulated others to study the interactions between ethanol and endogenous opioid mechanisms in animal models.

Goldstein and Judson[93] attempted to verify Davis and Walsh's hypothesis by administering escalating doses of naloxone up to 100 mg/kg to ethanol-addicted mice. They were unable to elicit opioid withdrawal symptoms and concluded that ethanol dependence is not caused by an endogenous opioid. In contrast, Blum et al[94] administered naloxone to mice and were successful in preventing ethanol addiction and withdrawal convulsions. Naloxone was also shown to block ethanol's effect of depleting brain calcium in this study[94] and in rats.[95]

Despite early optimism for using naloxone to prevent the psychomotor effects of low doses of ethanol in humans,[96] subsequent studies have been unable to show any such effects.[97-99] However, one study showed a decrease in nystagmus caused by the ingestion of ethanol.[100]

Case reports have described the dramatic reversal of ethanol intoxication in some patients.[101-103] Jefferys et al[104] administered naloxone 0.4 to 1.2 mg to 100 patients with suspected ethanol intoxication. A total of 20 patients responded with complete reversal of coma, and 5 responded partially. Of the 25 responders, 12 tested positive solely for ethanol on toxicology screening tests. Unfortunately, ethanol was confirmed only in responders, so one cannot determine whether nonresponders represented a special subset of ethanol users or whether they coingested other substances. The investigators speculated that responders may represent an enkephalin-sensitive group, because 10 of the 12 patients who tested positive showed a chlorpropamide-induced facial flush that was blocked by naloxone. Evidence against a general analeptic action was provided by a prospective study by Guerin and Friedberg.[105] Twelve patients with only ethanol ingestion regained normal consciousness after receiving 0.4 to 0.6 mg naloxone IV, whereas 23 with combined ethanol and benzodiazepine intoxication or barbiturate intoxication did not.

In a review article of naloxone use in ethanol intoxication, Dole et al[106] attempted to reconcile the dramatic effects cited in case reports with largely negative experimental data. In addition to higher serum ethanol levels, the frequent presence of coingestants seen clinically, and interspecies differences, they postulated that at least some of naloxone's effects may have resulted from improvement in blood pressure and cerebral perfusion. Faced with an individual patient intoxicated with ethanol, it may be worth trying naloxone to prevent the need for endotracheal intubation.

Shock

The endogenous opioid β-endorphin causes hypotension when injected parenterally[107] and is released from the pituitary concomitantly with adrenocorticotropin (ACTH) during stress.[108,109] These findings have led researchers to investigate the role of endogenous opioids in the pathophysiology of shock.

Septic Shock

Studies in mice, rats, dogs, and pigs have shown that naloxone is effective in septic shock. In general, large doses were used (>1 mg/kg), and treatment was most successful when naloxone was used before the initiation of sepsis or very early in the course of the disease. Several studies showed prolonged survival[110,111] or improved group rates of survival[112,113] in naloxone-treated dogs and rats. In dogs, there were also improvements lasting up to several hours in mean arterial pressure (MAP), cardiac output (CO), and left ventricular contractility (LV dP/dt), without changes in systemic vascular resistance (SVR) or pulmonary artery wedge pressure (PAWP).[112,114-116]

In addition to these cardiovascular changes, naloxone increased blood glucose,[111] serum pH,[111,117] and gastric epithelial cell oxygen tension.[117] Naloxone also prevented the hemoconcentration, decrease in leukocytes, and decrease in platelets in mice;[118] and prevented the hemoconcentration[111] and attenuated the bloody diarrhea associated with sepsis in dogs.[112] In septic piglets, intrapulmonary shunt fraction and physiological dead space were decreased, and ventilatory depression was reversed.[119]

Human studies have generally shown similar cardiovascular findings (improved MAP, CO, LV dP/dt, no change in PAWP),[120-122] but the results have been less impressive, perhaps because of the late presentation of many patients. Nevertheless, positive effects have been shown. For example, Groeger et al[123] found that 5 of 10 adult patients responded favorably to 0.3 mg/kg naloxone by increasing MAP. Responders had shorter duration of hypotension and lower serum lactate levels before treatment. However, there was no improvement in survival. Similarly, Safani et al[122] found that the five adults who responded to naloxone (0.03 mg/kg bolus, 0.06 mg/kg/h infusion) had a shorter duration of shock (7 hours) than the six patients who failed to respond (15.5 hours). Furthermore, 100% of patients who responded to naloxone survived compared with 0% survival in the nonresponders, but these data are confounded by the shorter duration of shock in the naloxone responders and the more common use of steroids in the naloxone group than in the placebo group. In contrast, Hackshaw et al[124] only found increased blood pressure without improvement in cardiac output or survival after administering naloxone (0.03 mg/kg bolus, 0.2 mg/kg/h infusion) for 1 hour to 13 adults with septic shock.

Hughes et al[120] administered a 0.03 mg/kg naloxone bolus followed by a 0.03 mg/kg/h infusion for 1 hour to eight adult patients with underlying malignancies and septic shock. The administration of naloxone resulted in improved blood pressure and left ventricular stroke work index (LVSWI) and lower serum lactate levels. Three of the eight patients survived. Septic shock was caused by gram negative, gram positive, and fungal pathogens.[121] Naloxone 0.01 mg/kg bolus followed by 0.1 mg/kg 30 minutes later improved blood pressure and LVSWI when combined with methylprednisolone. Plasma epinephrine levels were elevated by naloxone alone. Survival data were not presented.

Peters et al[125] administered naloxone 0.4 to 1.2 mg to 11 adult patients with septic shock. Eight of the nine patients without preexisting corticosteroid use responded dramatically with improved blood pressures; four patients also had improvements in mental status. In one patient with a thermal dilution catheter, cardiac output increased by 36%. Two patients had repeat doses and again had dramatic increases in blood pressure. Three patients ultimately survived. Four patients with adrenal insufficiency (three receiving high-dose corticosteroids and one with pituitary insufficiency) did not respond to naloxone. Presumably, ACTH and β-endorphin were not elevated by stress in these patients because of pituitary insufficiency or exogenous steroid use, and therefore, naloxone was not effective. Alternatively, an intact adrenal cortex may be necessary for naloxone's beneficial effects.[121,125,126]

Putterman et al[127] administered naloxone 0.4 to 1.2 mg to seven adults with eight episodes of sepsis within 2 hours of the onset of shock. All of the patients exhibited an increase in blood pressure and urine output for at least 1 hour after naloxone. However, only one patient survived to discharge.

In contrast to these uncontrolled case series, DeMaria et al[128] were unable to show a beneficial effect of naloxone 0.4 to 1.2 mg in a prospective trial for the treatment of septic shock. However, the study was small (23 episodes in 22 patients) and, therefore, had a low power to detect a difference between groups, and invasive hemodynamic monitoring was not performed.

There have been no controlled clinical trials of naloxone for the treatment of sepsis in children. Nevertheless, three case reports described the apparently successful use of naloxone in doses of 0.01 to 0.05 mg/kg in infants and children with septic shock caused by *Neisseria meningitidis, Escherichia coli,* and Group B streptococcus.[129-131]

Hemorrhagic Shock

Beneficial effects have been shown in many different animal models of hemorrhagic shock. Improvements were noted in left ventricular contractility, stroke volume, CO, MAP, and survival in dogs.[132-134] Similar results were obtained using naltrexone.[135] Naloxone was as effective as reinfusion of shed blood in restoring renal and hepatic blood flow and ensuring survival to 180 minutes in hemorrhaged dogs.[136] In another study, renal function and survival after kidney transplant were improved if hemorrhaged dogs received naloxone before transplant.[137] All of these studies used a reservoir model in which hemorrhage was induced to achieve and maintain a predetermined blood pressure (generally 40% to 60% of normal) by continuous adjustment of the circulating blood volume via the reservoir.

Naloxone restored the ability of nephrectomized cats to maintain blood pressure after a fixed volume hemorrhage; the effect was less pronounced in intact animals.[138] When

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