CURRENT CONCEPTS ABOUT THE TREATMENT OF SELECTED POISONINGS: Nitrite, Cyanide, Sulfide, Barium, and Quinidine

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The hospital and the research laboratory are both important sources of information in clinical toxicology. New knowledge based on recent observations has important implications in treating poisoning by barium, quinidine, methemoglobin-generating chemicals, and inhibitors of cytochrome oxidase. Based on this knowledge, suggestions are offered for the clinical management of these kinds of intoxications. This review emphasizes departures from established forms of therapy. For information about other aspects of the clinical management, a comprehensive treatise such as that by Gosselin et al (1) should be consulted.

Because methemoglobinemia and cytochrome oxidase inhibition cause defects in oxygen transport and utilization respectively, the role of pure oxygen in treating these disorders has long attracted attention. Recent experimental data indicate that hyperbaric oxygen is useful in treating some kinds of toxic methemoglobinemias and is dangerous in other kinds. Similarly, oxygen therapy may have some value against some cytochrome oxidase inhibitors (cyanide) and not others (sulfide). Of the many exogenous chemicals known or suspected to interfere with potassium metabolism, barium and quinidine have been selected for review. Current evidence indicates that the administration of K^+ can be life saving in barium poisoning. In quinidine poisoning K^+ plays a more limited and selective role.

NEW ROLES FOR OXYGEN

Management of Nitrite Poisoning

Until recently no important distinctions were recognized between techniques for the management of methemoglobinemia induced by nitrite salts on the one hand or

aniline and its congeners on the other. There has been rather limited experience with exchange transfusion as a general approach to the management of toxic methemoglobinemias (2). The potential advantage of reducing the blood concentration of both the offending chemical and the inert blood pigment simultaneously must be weighed against the risks of multiple transfusions. Alternative recommendations for treating methemoglobinemias have included the administration of ascorbic acid, oxygen at normal and hyperbaric pressures, and methylene blue (3).

The administration of ascorbic acid is attractive because of its extremely low toxicity; human poisonings are unknown (1). Unhappily, its safety is equaled by a lack of efficacy. In otherwise normal human erythrocytes made methemoglobinemic by in vitro exposure to chemicals, concentrations of ascorbate much higher than one could reasonably expect to achieve in the blood of patients did not significantly accelerate methemoglobin reduction (4). Thus, in normal individuals ascorbate offers no advantage over spontaneous methemoglobin reduction. In rare individuals born with an inherited deficiency of methemoglobin reductase, ascorbate administration is accompanied by a slow reversal of the congenital methemoglobinemia. In these and normal patients, however, ascorbate would be a poor choice for a life-threatening exposure to a methemoglobin-generating chemical.

Pure oxygen at atmospheric pressure is often mentioned as a therapeutic adjuvant to the management of acquired methemoglobinemia. Hyperbaric oxygen has been recommended on empirical grounds; we have not encountered published accounts of its use with human patients. Rats given lethal doses of sodium nitrite and exposed to 4 atm of pure oxygen had significantly lower blood methemoglobin concentrations and a lower mortality than groups exposed to air at 1 atm (5). Surprisingly, when the methemoglobinemia was induced by *p*-aminopropiophenone (PAPP), exposure to 4 atm of oxygen increased both blood methemoglobin and PAPP concentrations over that in animals maintained under air at 1 atm (6).

The above observations suggest that the effect of high pressure oxygen (HPO) in potentiating the methemoglobinemia after PAPP is mediated through an interference with the detoxication of PAPP by conjugation reactions such as acetylation of the amino group (6). If that hypothesis is true, HPO may generally potentiate methemoglobinemias due to aniline-like compounds. At least one other example is known. The avicidal compound, 3-chloro-4-methylaniline (3-CPT), generated significantly higher levels of methemoglobin in mice exposed to HPO than in mice exposed to air at 1 atm (7). This potentiation of the methemoglobinemic response, however, was not accompanied by an increase in mortality. Perhaps mortality was not increased because, like many aniline congeners, 3-CPT lethality in rodents appears to be unrelated to methemoglobinemia (7, 8). The oxygen pressures used in the experiment described above are higher than can be tolerated safely by human subjects, but pending further investigation it would appear prudent to avoid HPO in acute poisonings by aromatic amines (and nitro compounds?). In human nitrite poisoning HPO appears to deserve a clinical trial. No adverse effects of oxygen at 1 atm on either type of methemoglobinemia have been recognized in the laboratory or in the clinic to date.

At present the most widely accepted treatment of toxic methemoglobinemia is the administration of methylene blue. Its efficacy is firmly established, and a broad base

of clinical experience exists. It has been suggested, however, that a similar compound, toluidine blue, may have some advantages in terms of greater potency, more rapid onset of action, and fewer side effects (9).

In certain rare circumstances methylene blue has failed as an antidote against a chemically induced methemoglobinemia. One such case involved methemoglobinemia in an individual with an inherited deficiency of glucose-6-phosphate dehydrogenase (10). In this case the dye was without effect on the rate of methemoglobin reduction. It is effective, however, in red cells deficient in methemoglobin reductase (see above). Under some conditions methylene blue can attenuate the methemoglobinemic response of mice to 3-CPT but can significantly increase the mortality (7). It is not clear whether 3-CPT is unique among aniline derivatives in this respect or whether this type of interaction occurs only in rodents.

As tested in mice against nitrite poisoning, the combination of oxygen and methylene blue had at least additive effects in reducing mortality. At a low dose of methylene blue, oxygen at 2 atm was superior to oxygen at 1 atm, which in turn was superior to air at 1 atm. When the dose of methylene blue was increased, the advantage of HPO was lost, but oxygen at 1 atm was still superior to air at 1 atm (11).

Management of Cyanide, Sulfide, and Azide Poisonings

For many years it has been generally accepted that all of the toxic effects of cyanide are due directly or indirectly to an inhibition of cytochrome oxidase. The principles underlying the management of cyanide poisoning are well known (e.g. reference 1) and are directed toward increasing the rate of biological inactivation of cyanide. A moderate dose of sodium nitrite is injected intravenously to convert a tolerable fraction of the circulating blood pigment to methemoglobin. The latter traps and inactivates free cyanide by forming the stable complex, cyanmethemoglobin. Nitrite administration is followed by an intravenous injection of sodium thiosulfate. Thiosulfate furnishes sulfur for a reaction mediated by the enzyme rhodanese, which converts cyanide to the much less toxic thiocyanate.

The rhodanese reaction is insensitive to oxygen (12), and, as noted above, HPO acts to decrease methemoglobin levels after nitrite. The biochemical lesion in cyanide poisoning is one that prevents oxygen utilization instead of impairing its transport. For all these reasons, the administration of oxygen would appear to be superfluous in cyanide poisoning as long as the circulation is not compromised.

In accord with the above expectation even HPO failed to protect mice against death after cyanide or to reverse the course of cyanide poisoning. Moreover, HPO failed to have a significant effect on the anti-cyanide activity of either nitrite or thiosulfate (13). Both HPO and oxygen at 1 atm, however, significantly potentiated the anti-cyanide activity of the nitrite-thiosulfate combination (13–15). The magnitude of the potentiation was the same for oxygen at 1 and 4 atm, i.e. there was no advantage to HPO.

Extensive studies on respiratory, cardiovascular, and other physiological parameters in cyanide-poisoned dogs given nitrite, thiosulfate, and oxygen in various combinations failed to reveal a basis for the potentiating effect of oxygen. Oxygen alone

was able to reduce the length of the period of electrical silence of the EEG after cyanide. Although nitrite alone had a similar effect, thiosulfate alone appeared to prolong this period. In each case when oxygen was added (to nitrite, thiosulfate, or the combination), a decrease in the period of electrical silence was observed relative to that in air. No combination of treatments, however, was superior to oxygen alone (16). Clearly, these effects on the EEG do not match the pattern observed in the mortality of mice. However, the potentiating effect of oxygen on the antidotal action of the nitrite-thiosulfate combination has not been demonstrated in dogs as it has been in mice.

When mice were given large but sublethal doses of cyanide, a decrease in the respiratory excretion of $^{14}CO_2$ derived from previously administered uniformly labeled ^{14}C-glucose was observed. This response was identical in mice exposed to air or to oxygen at 1 atm, nor did the addition of either nitrite or thiosulfate result in significant changes in this response. The combination of oxygen with nitrite and thiosulfate, however, did result in a striking enhancement of cyanide-inhibited glucose metabolism (17). These effects of oxygen on glucose metabolism closely match the pattern of the effects on mortality, but they may represent a result of the oxygen effect rather than its cause.

Isom & Way believe that the synergistic effect of oxygen on the nitrite-thiosulfate combination cannot be due to an enhancement of cyanide detoxification because the measured blood cyanide levels in treated animals were several times higher than those in control groups (17). Exception must be taken to that conclusion, however, since the method used to determine blood cyanide concentrations almost certainly measures the total blood cyanide, including a large fraction that is bound in the biologically inactive form of cyanmethemoglobin (18). Thus, it remains to be established whether the free and biologically active fraction of the blood cyanide in treated animals is higher, lower, or substantially the same as in untreated animals.

It has been suggested that the mechanism of acute sulfide poisoning (whether inhaled as hydrogen sulfide or injected as sodium sulfide) also involves an inhibition of cytochrome oxidase. Thus, sulfide poisoning would be expected to resemble cyanide poisoning in many important respects. Accordingly, sodium nitrite protects a variety of animal species against death in acute sulfide poisoning presumably by trapping sulfide as sulfmethemoglobin (19–23). Sulfmethemoglobin is a dissociable complex in which the hydrosulfide anion is attached to ferric heme groups on methemoglobin. It seems to have no relationship to so-called sulfhemoglobin, which is a poorly characterized, irreversible, abnormal blood pigment sometimes seen in association with methemoglobin.

An antidotal effect of intravenous nitrite has been demonstrated in mice after their exposure to otherwise lethal concentrations of hydrogen sulfide in air (24) and of intraperitoneal nitrite in rats after injection of sodium sulfide (24a).

Possible interactions between oxygen, nitrite, and thiosulfate in acute sulfide poisoning have been explored (24a) using an experimental protocol that closely follows the one that uncovered the potentiating effect of oxygen as a cyanide antagonist (14). In accord with the findings for cyanide, oxygen at 1 atm did not protect

mice against acute sulfide poisoning when compared with animals maintained in air at 1 atm. Thiosulfate alone given to mice maintained in oxygen or air produced a small but statistically significant protective effect against death due to sulfide. A much larger protective effect was observed with nitrite, which was equally efficacious in animals exposed in air or oxygen. In marked contrast to the findings with cyanide, oxygen failed to potentiate the protective effects of the nitrite-thiosulfate combination.

Thus, it may be inferred that the potentiating effects of oxygen as a cyanide antagonist cannot be mediated through any mechanism that is also common to sulfide poisoning. For example, oxygen cannot be acting to increase methemoglobin levels by some unknown mechanism because such an effect would also be reflected in a change in the mortality after sulfide. Similarly, if oxygen in some way enhanced the pulmonary excretion of hydrogen cyanide gas, it would be expected to have a similar effect with volatile hydrogen sulfide. If indeed the mechanisms for acute poisoning are the same for cyanide and for sulfide, the effect of oxygen in the case of cyanide would most likely be manifested through some metabolic inactivation mechanism that is not available to sulfide. If this were a sluggish pathway in which a fivefold difference in oxygen tension could result in significant differences in rate, the role of nitrite and thiosulfate might simply represent a delaying action such that this pathway might find expression.

For a given circulating level of methemoglobin, a greater protective effect is seen against cyanide than against sulfide, a result that correlates with estimates of the relative stability of the respective anion-methemoglobin complexes (20). Nevertheless, the protective effect of nitrite in acute sulfide poisoning is significant, and this agent deserves a trial in an acute human poisoning. Oxygen can do no harm as an adjuvant, and in the case of cyanide poisoning treated with nitrite-thiosulfate it may significantly increase the antidotal effect.

A very small but statistically significant protective effect of nitrite against acute azide poisoning was also observed in mice (25). Again the magnitude of this effect correlated with the stability of the azide-methemoglobin complex relative to that of the cyanide and sulfide complexes (20). Because no other antidotes to azide poisoning are known and because azide has a high toxicity, a clinical trial with nitrite was recommended. A single remarkable case has now been reported (26). A woman ingested an unknown amount of sodium azide, and after 90 minutes fainted with complaints of loss of vision and nausea. Within a few hours the clinical picture was dominated by pulmonary edema, lactic acidosis, and hypothermia. Among other measures she was given amyl nitrite by inhalation, sodium nitrite by vein, and intranasal oxygen. A clear-cut elevation of methemoglobin levels was documented, but the patient died in shock in 12 hours. Thus, in its only clinical trial, nitrite failed to produce obvious clinical benefit in acute azide poisoning, and a search for more effective antidotes is indicated. Two points might be made, however, the first being that the procedure did no obvious harm and the second being that the patient survived 12 hours. Mice given lethal doses of azide parenterally often expire within 5 minutes; it is conceivable that nitrite might have delayed death in this case.

THE ROLE OF POTASSIUM

Management of Barium Poisoning

Whereas human poisonings by soluble barium salts are uncommon, isolated accidental and suicidal ingestions are reported with surprising frequency (e.g. 27–29). Epidemics have also been described. In the early 1940s an endemic state of barium intoxication arose in a Chinese province due to the contamination of table salt with barium chloride (30, 31). Flour containing barium carbonate poisoned 85 British soldiers in India (32). An outbreak of severe food poisoning involving 100 individuals in Israel was traced to sausage contaminated with barium carbonate (33).

Barium ion stimulates smooth, striated, and cardiac muscle; the result is violent peristalsis, arterial hypertension, muscle twitching, and disturbances in cardiac action. Motor disorders include stiffness and immobility of the limbs and sometimes of the trunk, leg cramps, twitching of facial muscles, and paralysis of the tongue and pharynx with attendant loss or impairment of speech and deglutition (34). The central nervous system may be first stimulated and then depressed (32). Small amounts in cerebrospinal fluid induce convulsions (35). Ventricular tachyarrhythmias (including ventricular fibrillation) and transient asystole have been observed (36). Kidney damage has been described as a late complication, presumably a result of circulatory insufficiency (37). Probably the most distinctive effect of barium in large doses, however, is skeletal muscle weakness and eventually flaccid paralysis involving extremities and respiratory muscles (30–32, 38).

In an experimental study in rats, Schott & McArdle (39) demonstrated that barium-induced paralysis was due to a defect in muscle itself. During intravenous infusions of $BaCl_2$ (cumulative doses of about 20 mg/kg), curarized rat leg muscles stimulated electrically produced twitches with amplitudes that were transiently increased and then greatly attenuated. At the same time the plasma level of potassium fell rapidly to about 2 meq/liter. The partial paralysis correlated with the hypokalemia much better than with the plasma barium concentration. The plasma sodium level was unaffected.

Hypokalemia in barium-poisoned humans was probably first described by Diengott et al (40). Two severely poisoned patients, one of whom had experienced no vomiting or diarrhea, were found to have plasma K^+ levels of 2.0 and 2.4 meq/liter. Both responded clinically to intravenous KCl, although one eventually died from severe pulmonary edema and hemorrhagic gastritis and duodenitis. This episode confirms the dramatic relief of symptoms described by Huang (38) in two victims of barium poisoning treated with intravenous potassium citrate. Huang was impressed with similarities between barium intoxication and the rare disorder known as familial periodic paralysis. Features of the two states have been compared (39).

The mechanism of barium-induced hypokalemia has not been completely clarified. Enhanced renal excretion does not appear to be responsible (41). The rapidity of the fall in plasma potassium suggests that K^+ migrates into tissue cells. Presumably muscle cells are involved, but the phenomenon has been demonstrated in vivo only with dog red blood cells (41). Whereas epinephrine secretion from the adrenal medulla is provoked by barium (42) and this hormone can promote an accumulation

of K^+ in cells (43), barium-induced hypokalemia cannot be ascribed to epinephrine because it cannot be prevented by adrenergic blockers such as phentolamine (41) or propranolol (39). A direct action of barium on muscle is inferred. Perhaps it activates Na^+-K^+-stimulated ATPase at cell surfaces to promote K^+ entry at the expense of the extracellular stores (44). In isolated frog muscle, however, it did not modify the K^+ content, but it did decrease inward and outward K^+ permeability constants equally (45).

In poisoned rats, infusions of K^+ (but not of Ca^{2+}) corrected promptly both the hypokalemia and muscle weakness (39). In dogs (41), all signs and symptoms of barium poisoning except hypertension were responsive to the administration of K^+; specifically, muscle weakness, diarrhea, and cardiac arrhythmias were alleviated. Whatever the mechanism of the hypertension, neither K^+ nor adrenergic blocking drugs suppressed it. As noted above, clinical experience with potassium therapy has also been favorable (33, 38), and at times the benefits have been spectacular. Large parenteral doses, however, may be required; in recent reports of acute barium poisoning in three adults (28, 29, 36), the cumulative dose of K^+ administered over the first 24 hr was 420, 260, and 250 meq, respectively.

Thus, potassium administration is judged to be a rational and effective form of treatment for barium poisoning. Although the recommendation is over 30 years old, it apparently is not widely recognized by clinical toxicologists. In any case barium's ability to induce hypokalemia and paralysis is not shared by strontium or any other alkaline earth element (1).

Management of Quinidine Poisoning

Quinidine also induces derangements of K^+ metabolism, as do several other antifibrillatory drugs. The cellular actions of quinidine on ion fluxes are better defined than those of barium, but they also appear to be more complex. Even with little or no change in the resting transmembrane potential, quinidine reduces myocardial sodium influx and potassium efflux during systole, diastole, or both (46–48). At the same time the K^+ influx may be enhanced (46, 49). In several experimental preparations (e.g. isolated atria, excised papillary muscles, perfused hearts), these permeability changes have led to significant increases in the myocardial content of potassium (48, 50), although this is not a universal finding (51).

Presumably other organs and tissues also extract K^+ from the extracellular fluid under the influence of quinidine. At least mild hypokalemia that cannot be accounted for by K^+ losses in vomitus or feces has been described in several cases of poisoning by quinidine (52, 53) and quinine (54). A low plasma K^+ level, however, has not been reported often in these conditions; perhaps the tendency to hypokalemia is masked by extraneous factors commonly associated with quinidine usage, such as the chronic intake of digitalis, poor circulatory reserve, defective renal excretion, and respiratory acidosis. In any case the clinical toxicity of quinidine, unlike that of barium, cannot be explained by any simple defect in K^+ metabolism.

Signs and symptoms of quinidine poisoning are referable to the central nervous system, gastrointestinal tract, blood vessels, and heart (1). In clinical poisonings the most dangerous effects are usually those on the heart. It is important for the

therapist to recognize that the cardiotoxicity of quinidine can assume two distinct forms. The first pattern (Type I) involves a failure of cardiac stimulus formation or propagation, terminating in ventricular standstill. The second pattern (Type II) is one of abnormal stimulus formation, leading to ventricular tachyarrhythmias and terminating in ventricular fibrillation. Although the terminology used here is not well established, the distinction is believed to be important because the two situations demand entirely different programs of therapy. The two patterns of toxicity also have different implications with respect to potassium.

Stimulus failure (Type I) can be regarded as a progressive state involving a weakening of impulse formation (pacemaker failure) and a gradual impairment of conduction, particularly through the specialized conducting system of the atrioventricular (AV) junction and ventricles. A lengthening of the QRS interval by 50% or more (120 to 140 msec or longer) is sometimes regarded as a sign that vigorous measures may be required to sustain the cardiac beat (55). Perhaps an infusion of 1 molar sodium lactate is useful under these circumstances (56), but probably one of the catecholamine drugs is preferable. Epinephrine, norepinephrine (levarterenol), and isoproterenol are all capable of stimulating atrial pacemakers and of narrowing a wide QRS complex or of accelerating a slow idioventricular pacemaker in the presence of complete heart block. They also increase the stroke volume and cardiac output by stimulating the quinidine-depressed myocardium (57). At least in rats the lethality of quinidine is distinctly reduced (58). It has been asserted without proof that isoproterenol accomplishes these changes with a smaller risk of inducing ventricular tachycardia or fibrillation than does epinephrine (59). Because isoproterenol is a vasodilator and norepinephrine a vasoconstrictor, the latter would appear to be preferable in the hypotensive patient. In quinidine-poisoned dogs, however, norepinephrine did not increase peripheral vascular resistance (57); the elevation in blood pressure was due entirely to cardiac stimulation.

If an infusion of isoproterenol or norepinephrine fails to sustain an adequate heart rate and stroke volume in Type I poisoning, electrical pacing of the ventricles may be indicated, but the attempt is apt to be unsuccessful because of the high threshold of the quinidine-poisoned heart (52). Certainly all antifibrillatory drugs should be avoided. Except in cases of severe hypokalemia (see above), even potassium should be withheld. Thus, quinidine and potassium induce similar aberrations of the ECG, and mild hypokalemia protects dogs against quinidine-induced intraventricular conduction failure and raises the lethal dose of quinidine (60). Survival of a 42-year-old woman who ingested 100 coated (long-acting) tablets of quinidine sulfate (total dose 20 g) was ascribed (perhaps wrongly) to hypokalemia produced by hemodialysis (61).

In contrast, the abnormal mechanism of ventricular activation in Type II poisoning usually involves a rapid heart rate. The therapist's aim is to moderate and control the ventricular tachycardia and to prevent its deterioration into ventricular fibrillation. Under these circumstances potassium may be a useful agent, and it has been infused in victims of quinidine poisoning (52, 53). Except when used to correct preexisting hypokalemia, however, potassium should probably be discarded in favor of an antifibrillatory drug that is less apt to compromise AV conduction. Both

propranolol (62) and lidocaine (63) have been used successfully to terminate ventricular rhythms in quinidine poisoning and to restore a supraventricular mechanism. Diphenylhydantoin sodium would probably be superior to propranolol and perhaps to lidocaine under these circumstances. Ventricular fibrillation may necessitate defibrillation by direct current electroshocks (64), but ventricular contractions may resume spontaneously after brief, recurring periods of fibrillation (65).

To employ these therapeutic regimens correctly, it is necessary of course to recognize both types of poisoning and to distinguish between them. In practice it is sometimes difficult to differentiate between ventricular tachycardia (Type II) and a supraventricular mechanism with bundle branch block or other conduction defect (Type I) (66). Furthermore, clinical signs of both patterns can sometimes be found in a single person. For example, Type I patients occasionally exhibit ventricular premature beats (52, 53), and Type II patients often show widening of the QRS complex before a ventricular mechanism becomes established (65). To predict the ultimate or definitive pattern, one notes that persons with chronic heart disease, especially in congestive failure, usually exhibit a Type II reaction to quinidine overdoses (66). In persons with structurally sound hearts, Type I is thought to be the more common pattern (52, 61). Even when quinidine caused ventricular tachycardia in otherwise healthy hearts, the disorder was well tolerated and fibrillation did not occur (53, 66).

CONCLUSIONS

In certain types of uncommon human poisonings, the therapist must be prepared to act on the basis of experimental findings in animals. Recent laboratory evidence suggests that hyperbaric oxygen is an effective antidote to nitrite poisoning but that it should be avoided in poisonings with aniline and its derivatives. Pure oxygen at atmospheric pressures potentiates the antidotal activity of a nitrite-thiosulfate combination against cyanide. Although oxygen appears to do no harm in acute hydrogen sulfide poisoning, it is not useful, but nitrite has significant protective and antidotal effects. Despite a marginal protective effect of nitrite against azide poisoning in mice, it was not efficacious in a single human intoxication. Both experimental and clinical evidence indicates that barium modifies the cellular distribution of potassium and that K^+ is a valuable agent in the management of barium poisoning. Quinidine also influences the metabolism of potassium, but more observations are required to clarify the roles of K^+ in the pathogenesis and treatment of quinidine poisoning.

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