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Photodegradation of Sodium Nitroprusside: Biologic Activity and Cyanide Release

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Because the belief that cyanide is released from nitroprusside *in vivo* recently was challenged, the authors performed a series of experiments that examined the conditions under which nitroprusside is degraded. These experiments include an examination of the release of cyanide and nitric oxide from nitroprusside *in vitro*, the release of cyanide *in vivo*, and a comparison of the biologic activity of intact and degraded nitroprusside. Nitroprusside in aqueous solution degraded when exposed to white or blue light but not to red light. While light at 20 $\mu W \cdot cm^{-2}$ produced 40% apparent photodegradation after 6 h exposure, while white light at 220 $\mu W \cdot cm^{-2}$ produced 100% apparent photodegradation after 2 h exposure. At 100% apparent photodegradation, 10% of the nitrosyl ligand was recovered as free nitric oxide, and 0.4% of the cyanide ligand was recovered as free cyanide. Following a 2-h infusion of light-protected nitroprusside in seven patients, cyanide concentrations ranged from 1.4 to 45.5 μM and 0.09 to 3.2 μM in blood and plasma, respectively. These values were not changed by exposing the samples to white light (220 $\mu W \cdot cm^{-2}$) for 4 h. Intact and photodegraded nitroprusside produced identical hypotensive responses in rats as would be expected, since the nitrosyl ligand was detected in solution following degradation, and it mediates this action. Cyanide was released from nitroprusside, both on its exposure to light *in vitro* and also *in vivo*. The latter was not an artifact of the assay for cyanide. Nitroprusside releases cyanide *in vivo*, and cyanide toxicity is a true complication of its use. (Key words: Anesthetic techniques: hypotension, induced. Blood pressure: drug effects. Pharmacology: nitroprusside. Toxicity: cyanide; nitroprusside.)

SODIUM NITROPRUSSIDE, $Na_2Fe(CN)_5NO$, administered intravenously, commonly is used to induce hypotension intraoperatively to reduce intravascular pressure and/or to decrease blood loss during surgery.[1] It also is of use in malignant hypertension and has been used to reduce systemic vascular resistance following myocardial infarction.[2] Although the drug has several virtues as a hypotensive agent, many investigators have expressed concern regarding the potential toxicity from cyanide, since the intact molecule contains five cyanide groups.[3-11] That cyanide is released from the molecule *in vivo* has been demonstrated by several investigators, some of whom believe that its site of release is in the red blood cells,[5,11] while others propose that the liver or other organs are the primary sites.[12]

Recently, Bisset *et al.* seemingly refuted earlier work by suggesting that "there is, to date, no unambiguous evidence that cyanide is released from nitroprusside in vivo" and further stating that "it may well be safe to infuse quantities larger than those currently recommended."[13] These authors argued that any cyanide detected in blood obtained from patients receiving nitroprusside resulted from photodegradation of the drug that occurred *in vitro*, either before its infusion or during assay of the samples for cyanide.[13] Bisset's report surprised us because of the pathophysiologic and chemical evidence of metabolic alterations consonant with cyanide toxicity that have been reported with nitroprusside. The work of Bisset *et al.*[13] was challenged in a letter by Vesey *et al.* as well.[14]

Bissett's report[13] stimulated us to identify the conditions under which cyanide is released from nitroprusside. Since the answer to this important question could have significant impact on the clinical use of sodium nitroprusside, we performed a series of human, animal, and chemical experiments to determine if cyanide release occurred only *in vitro* or whether its release also occurred *in vivo*. To answer the question, we posed four others: 1) Under what conditions is sodium nitroprusside degraded *in vitro*? 2) Is the cyanide that is measured in blood from patients receiving nitroprusside an artifact of the assay for cyanide? 3) Does degraded nitroprusside remain biologically active? 4) Is degraded nitroprusside more toxic than intact nitroprusside? Our findings, which constitute this report, confirm earlier observations that cyanide is released *in vivo* from nitroprusside.[5,15]

Materials and Methods

To examine its photodegradation, aqueous solutions of sodium nitroprusside (Sigma Chemical) ranging in concentration from 6.7×10^{-4} M to 2.0×10^{-2} M were exposed to light produced by an FC8T9CW fluorescent lamp contained in a small, well-ventilated chamber. The energy of the light incident on the samples was varied from 20 $\mu W \cdot cm^{-2}$ (equivalent to room illumination) to 220 $\mu W \cdot cm^{-2}$ by changing the distance between the sample and the light source. Illuminance was measured with a cadmium sulfide photocell and converted to units of microwatts per square centimeter.§ The wavelength

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of the light incident on some samples was varied with Kodak® Wratten filters (25 and 47B). The illuminance of the filtered light incident on the samples was made equal to that of the unfiltered control white light.§ The absorption spectrum of nitroprusside solutions was determined with a Beckman® 25 recording spectrophotometer. The same instrument was used for the colorimetric assays of cyanide and nitric oxide. The apparent photodegradation of nitroprusside was determined serially by observing its change in absorbance at 394 nm. Degradation as defined by Frank *et al.*[16] was calculated using the following formula:

$$\% \text{ Degraded} = \frac{(\text{molar absorptivity of sample} - 20.4)\P}{0.8}$$

The release of free cyanide from nitroprusside was determined by the method of Rodkey and Collison[17] in which solutions of nitroprusside were acidified to form HCN gas, which then was trapped in dilute alkali and quantified colorimetrically in a pyridine/pyrazolone complex. The release of free nitric oxide from nitroprusside was determined colorimetrically using 200-μl aliquots of the nitroprusside solution in an assay developed to detect gaseous oxides of nitrogen and modified to detect the same compounds in solution.[18,19] In this method, oxides of nitrogen in solution or the nitrite ion form an azo dye when mixed with diazotizing-coupling reagents (sulfanilic acid and N-[1-napthyl]-ethylenediamine dihydrochloride).[18] To clarify the extent of their releases from the nitroprusside molecule, the amounts of free nitric oxide and free cyanide detected are reported as a percentage of the total amount of each group contained in the nitroprusside molecule prior to its degradation by light.

To examine the release of cyanide *in vivo,* aliquots of blood were obtained from seven patients undergoing surgical correction of idiopathic scoliosis using hypotension produced by sodium nitroprusside to decrease blood loss intraoperatively. Infusion rates of the drug, which was protected from light, ranged from 2 to 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The sample from each patient was obtained immediately before terminating the 2-h infusion of nitroprusside. Previous studies from our laboratories have shown that the concentration of cyanide in blood should be greatest at this time.[20] Samples were collected in glass tubes containing Na_2 EDTA and wrapped with aluminum foil to prevent exposure of the blood to light. All subsequent sample handling, unless otherwise mentioned, was carried out at room temperature in a darkened hood (less than 1 $\mu W \cdot cm^{-2}$). Plasma was obtained by centrifugation. Some aliquots of blood and plasma were exposed to white fluorescent light (20 and 220 $\mu W \cdot cm^{-2}$) for 4 h, while others were kept free from light during this time. All samples of blood and plasma then were assayed for free cyanide. Statistical analysis of these data was done using a paired *t* test. The protocol that involved patients was approved by the Human Investigation Committee of the University of Virginia.

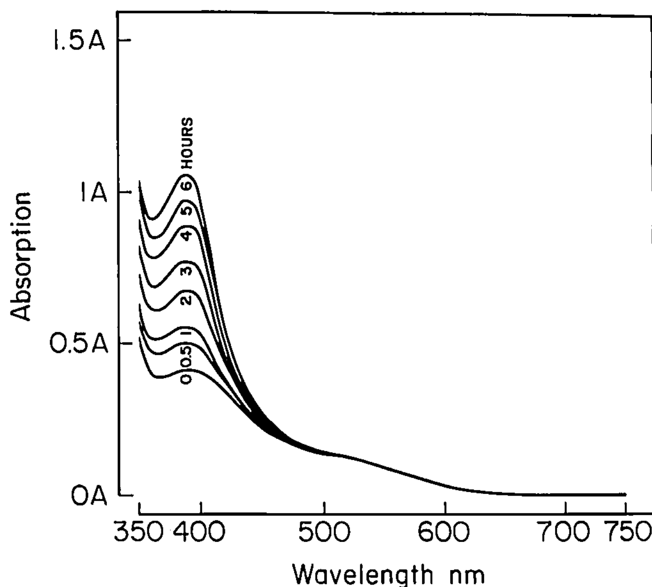

FIG. 1. Changes in absorption spectrum of 20 mM nitroprusside during its photodegradation by white light (20 $\mu W \cdot cm^{-2}$). Increasing absorption indicates increasing degradation. The numbers beneath each curve represent the duration of exposure of the sample to light in hours.

The hypotensive actions of intact and apparently photodegraded sodium nitroprusside were determined in eight Sprague–Dawley rats (300–400 g). Rats were anesthetized with pentobarbital (50 $mg \cdot kg^{-1}$ ip); a femoral vein was cannulated for administration of the drug; and a carotid artery was cannulated for determining blood pressure. Each rat received intravenous boluses of intact and photodegraded nitroprusside (200 $\mu W \cdot cm^{-2}$ for 2 h) ranging from 0.3 to 30 $\mu g \cdot kg^{-1}$ administered in a random sequence. The response to each bolus was recorded on a Gould chart recorder. Blood pressure was allowed to return to normal levels between each injection. Dose–response curves were constructed, and these data were analyzed by unpaired *t* tests.

Results

Sodium nitroprusside (20 mM) in aqueous solution degraded when exposed to white fluorescent light (20 $\mu W \cdot cm^{-2}$) (fig. 1). The magnitude of this degradation

¶ The absorption change is said to result from the shift of an electron from the d orbital of iron to the π orbital of the nitrosyl group. In keeping with the terminology of Frank *et al.*,[16] we have opted to use their term "degradation (see "Discussion").

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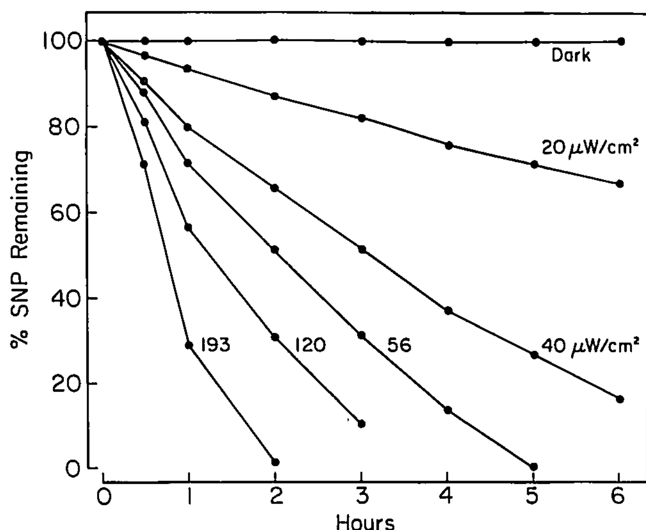

FIG. 2. Rates of apparent photodegradation of sodium nitroprusside by various energies of light incident on the samples. Normal room illuminance is about 20 $\mu W \cdot cm^{-2}$.

was dependent on the duration of exposure of nitroprusside to light. The increase in absorbance at 394 nm (previously reported by Frank *et al.*[16]) was used in subsequent experiments to calculate the extent of apparent

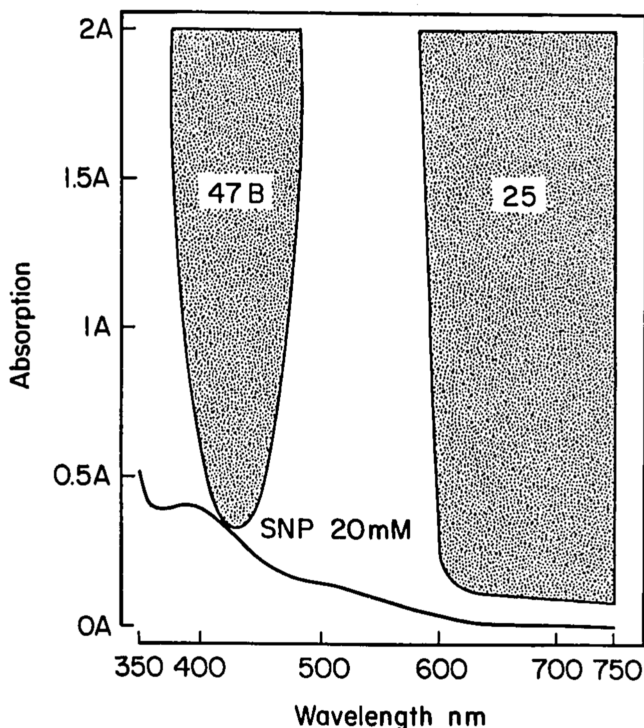

FIG. 3. The bottom curve represents the absorption spectrum of 20 mM nitroprusside. The shaded area on the left represents the wavelengths of visible light transmitted by a blue filter (Wratten 47B). The shaded area on the right represents the wavelengths transmitted by a red filter (Wratten 25).

degradation of nitroprusside as represented by the formation of an intermediate species (see "Methods" and "Discussion"). Similar behavior was observed with lower concentrations of nitroprusside.

Figure 2 shows the results of these calculations for the degradation of 20 mM nitroprusside by white light varying in illuminance from 20 to 193 $\mu W \cdot cm^{-2}$. The rate of apparent photodegradation was dependent on the energy of the light incident on the sample.

The absorption spectrum of intact nitroprusside (fig. 3) suggests that the agent should be relatively stable in red light, where it absorbs little light energy and unstable in green or blue light, the wavelengths of which it absorbs. To prove this hypothesis, we exposed 20 mM nitroprusside to white, red, and blue light and followed its apparent photodegradation with time. Under all three conditions, the energy of light incident on the samples was 20 $\mu W \cdot cm^{-2}$. The properties of the red (Wratten 25) and blue (Wratten 47B) filters used in these experiments and the regions of the absorption spectrum of nitroprusside attacked by light transmitted by these filters are shown in figure 3. Under these conditions, nitroprusside was stable during 6 h of exposure to red light (fig. 4). Its apparent degradation was 45% in white light and greater than 80% in blue light, as shown by changes in absorption at 394 nm (fig. 4). In the same experiments, essentially no free nitric oxide or free cyanide was liberated from nitroprusside that had been exposed to red light. In contrast, both of these groups were released by nitroprusside that had been exposed to white or blue light, with the greater release occurring during exposure to blue light (fig. 4).

The relationships between the extent of photodegradation of nitroprusside in white light at 20 and 220 $\mu W \cdot cm^{-2}$ and the appearance of both free nitric oxide and cyanide are shown in figure 5. There was a linear correlation between the release of nitric oxide and the extent of apparent photodegradation (r = 0.99). In contrast, the release of free cyanide increased exponentially with respect to photodegradation of nitroprusside (r = 0.95).

The concentrations of free cyanide in whole blood that resulted from a 2-h-long infusion of nitroprusside in seven patients ranged from 1.4 to 45.5 µM. Concentrations of free cyanide in plasma were about tenfold less and ranged from 0.09 to 3.2 µM. These cyanide concentrations were not changed significantly by exposing the samples of blood and plasma to white light (20 and 220 $\mu W \cdot cm^{-2}$) for 4 h (fig. 6). The concentrations of free cyanide determined in the infusate (50 mg nitroprusside in 250 ml of D5) following termination of the infusion ranged from 1 to 2 µM. Even assuming that free cyanide were limited in distribution to the circulating blood volume, the amount of free cyanide infused would account for less than 1% of the cyanide that we detected in blood.

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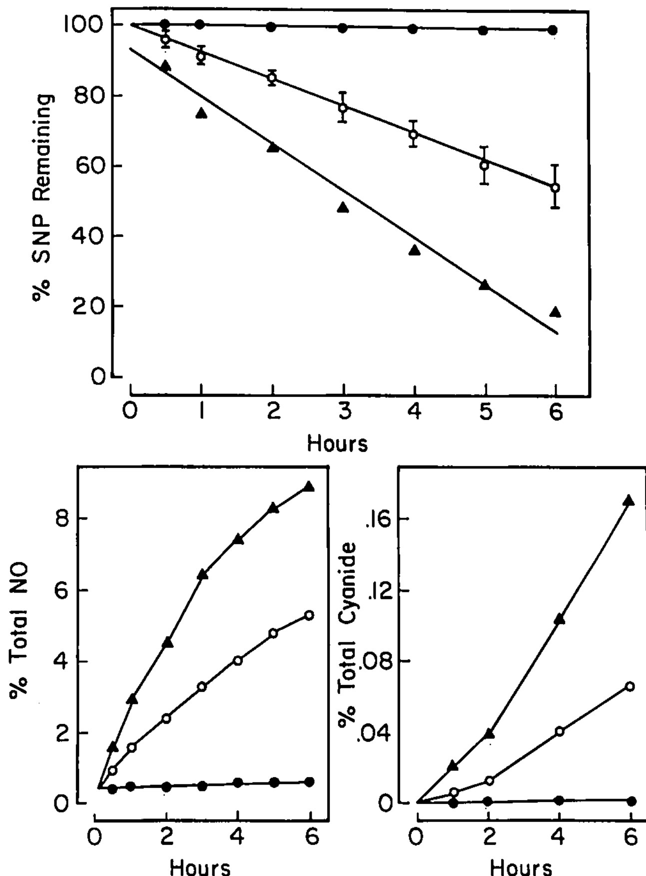

FIG. 4. The upper panel represents the apparent degradation of nitroprusside over time in red, white, and dark blue light (20 $\mu W \cdot cm^{-2}$). Degradation was calculated by the increase in absorbance of the solution at 394 nm (see "Discussion").[16] The bottom left panel represents the release of nitric oxide, and the bottom right panel represents the release of cyanide in the same experiments. The concentrations of nitric oxide and cyanide detected were compared with the total calculated concentrations of these groups in sodium nitroprusside before its degradation and are reported as percentage of the total calculated values. Closed circles, open circles, and triangles represent red, white, and blue light, respectively.

Intact and photodegraded nitroprusside, as determined by change in absorbance at 394 nm, were equally effective in producing hypotension in rats (fig. 7).

Discussion

PHOTODEGRADATION

Degradation of sodium nitroprusside by light involves a complex sequence of events and, as yet, is not understood completely.[16,21,22] A proposed scheme is shown in figure 8. According to Frank *et al.*,[16] the initial event is a photoexcitation of the bond between the nitrosyl moiety and iron in the molecule. Frank proposed that a photoexcited species (II) with a calculated molar extinction coefficient of 102 $M^{-1} \cdot cm^{-1}$ is responsible for the increase in absorbance at 394 nm shown in figure 1 and that this increase can be used to calculate apparent degradation of nitroprusside.[16] Thus, the extent to which nitroprusside is degraded as calculated by this formula is dependent upon the assumption that compound II is a single, relatively stable species said to be a photoexcited form of

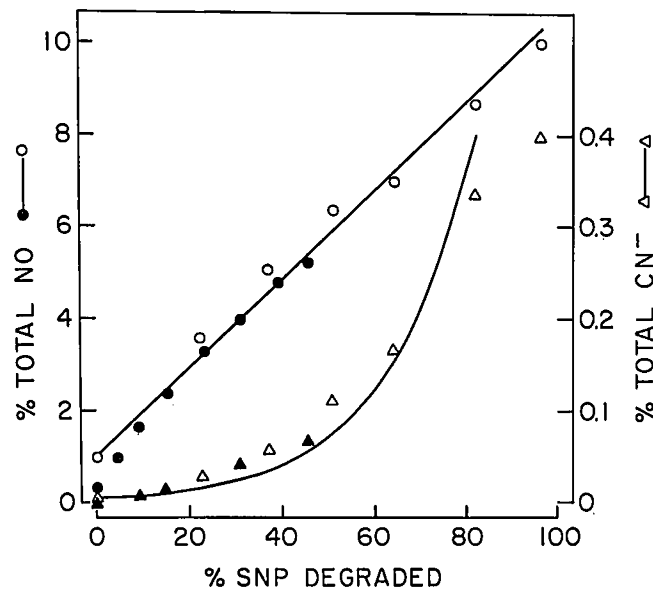

FIG. 5. The release of nitric oxide from nitroprusside increased linearly as photodegradation proceeded ($y = 0.0977 \times +0.9228$, $r = 0.99$), while the release of cyanide increased exponentially ($y = 0.0048e^{0.0539x}$, $r = 0.95$). Circles represent nitric oxide and triangles represent cyanide. Closed and open symbols represent degradation at 20 and 220 $\mu W \cdot cm^{-2}$, respectively.

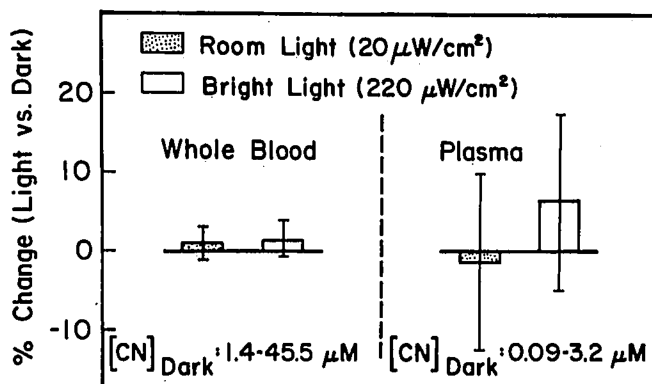

FIG. 6. Blood and plasma, obtained from seven patients receiving nitroprusside, were assayed for cyanide before and after the samples were exposed to light. The values for samples that were not exposed to light are shown at the bottom of the figure. The values for samples that were exposed to white light (20 or 200 $\mu W \cdot cm^{-2}$) for 4 h are shown as percentage change from those not exposed to light. Exposure of blood and plasma to light did not significantly change the concentration of free cyanide in these samples.

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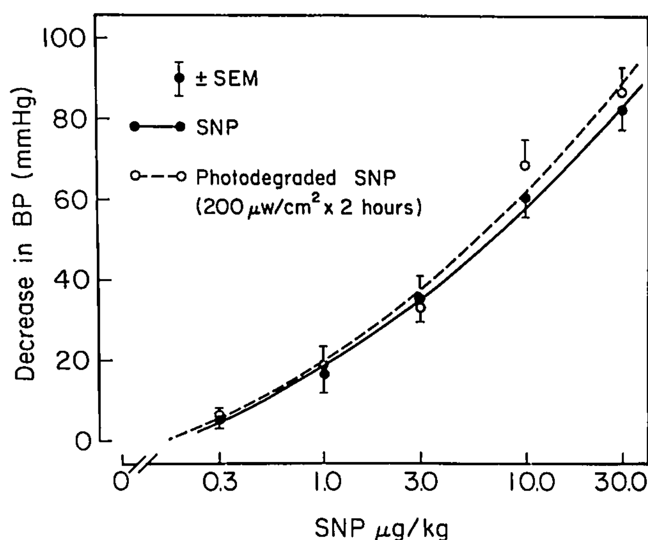

FIG. 7. Decreases in blood pressure were similar in rats that received bolus doses of intact and photodegraded nitroprusside.

nitroprusside $[Fe(CN)_5NO^*]^{-2}$.[16] It is more likely, however, that the spectrophotometric evidence attributed to a putative compound II results instead from a mixture of nitroprusside and compound III. We observed that 100% apparent photodegradation of nitroprusside released only 10% of the NO contained in the molecule (fig. 5). This strongly suggests that the degradation of nitroprusside was not complete. The molar extinction coefficients of nitroprusside and compound III are, respectively, 20.4 and 1,090 $M^{-1} \cdot cm^{-1}$.[16,23] The extinction coefficient of a solution resulting from a fractional conversion of nitroprusside to III would lie somewhere between these values and may explain the value attributed by Frank *et al.* to compound II alone.[16] Because of this uncertainty, we have chosen to use the term "apparent photodegradation." This explanation could account for the discrepancy between the extent of photodegradation we calculated using the increase in absorbance and the amount of free nitric oxide we detected in solution (fig. 4). Later steps are even less clear and involve, among other things, the complete separation of nitric oxide from the molecule.[21,22] In any case, exposure of nitroprusside

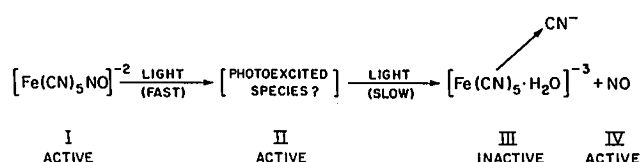

FIG. 8. The scheme of nitroprusside photodegradation modified from that proposed by Frank *et al.*[16] The molecules shown are as follows: I: nitroprusside; II: photoexcited species? (see "Discussion"); III: aquapentacyanoferrate; IV: nitric oxide. "Active" and "inactive" refer to the ability of each compound to relax vascular smooth muscle.

to light initially resulted in an increase in absorption at 394 nm[16] and subsequently resulted in the release of nitric oxide, forming compound III. The rate at which these events occurred was dependent upon both the energy of the light incident on the sample and the length of time the sample was exposed to light (fig. 2).

The degradation of nitroprusside in blue light, but not in red, was predictable from the absorption spectrum of nitroprusside. Similar behavior has been observed with monochromatic light at 366 and 436 nm.[22] Red light was not absorbed by nitroprusside (fig. 3), and it did not photodegrade the molecule.

BIOLOGIC ACTIVITY OF NITROPRUSSIDE

All of the photodegradation products of nitroprusside that remain active in lowering blood pressure or relaxing smooth muscle contain a nitrosyl moiety (fig. 8). The fact that this group is the portion of the nitroprusside molecule responsible for producing hypotension has been known since 1929.[24] For the nitrosyl moiety to function, it has been suggested that it must be released from the nitroprusside molecule. It has been demonstrated clearly, for example, that analogs of nitroprusside in which transition metals other than iron have been substituted (*e.g.*, Mo, W, Mn) are incapable of mimicking the ability of nitroprusside to inhibit platelet aggregation.[25] In addition, the manganese-substituted analog does not alter blood pressure when infused in rabbits, while the same dose of nitroprusside in an identical experiment lowers arterial pressure by 44%.[26] In these substituted analogs, the nitrosyl ligand is bound more tightly to the remainder of the molecule than in nitroprusside, and it is not released.[25] The breakdown products of nitroprusside that do not contain the nitrosyl moiety (*e.g.*, $Fe(CN)_5H_2O^{-3}$, $Fe(CN)_6^{-4}$, $Fe(CN)_6^{-3}$) do not produce hypotension when infused in rabbits.[25] Thus, it is clear that the availability of the nitrosyl moiety is essential to the hypotensive action of nitroprusside. Its release *in vivo* sets the stage for subsequent release of cyanide.

RELEASE OF CYANIDE FROM NITROPRUSSIDE *IN VIVO*

Although free cyanide was detected in blood obtained from patients receiving nitroprusside, the concentrations of cyanide were not increased further by exposing the blood to light. Since there was essentially no free cyanide in the infusate, and since it was not an assay artifact (fig. 6), the cyanide detected in blood had to have been released from nitroprusside *in vivo*. Not only did blood serve as an opaque medium to block the transmission of light, but it also may have served as a filter to prevent the transmission of other than red light, and thus protect the nitroprusside. Bisset *et al.* also observed no increase in free CN during light exposure of blood containing ni-

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troprusside that had been added *in vitro*.[13] We saw a tendency for increase in free cyanide in plasma exposed to white light (220 $\mu W \cdot cm^{-2}$) for 4 h (fig. 6), but this trend was not statistically significant.

Smith and Kruszyna[5] suggested that hemoglobin is responsible for removing cyanide from the nitroprusside molecule. In contrast, we saw no change in the concentrations of free cyanide in our blood samples that were stored at room temperature for 4 h in the dark. The lack of increase in cyanide concentrations in these samples suggests that hemoglobin did not remove cyanide from nitroprusside molecule by various molecules containing sulfhydryl groups including glutathione, free hemoglobin, and others, and by homogenates of liver and kidney.[5,9] Vesey *et al.*[27] demonstrated that during intravenous infusions or bolus injections of nitroprusside in dogs, the peak concentration of cyanide in plasma is attained prior to that in the red blood cell, implying that cyanide *in vivo* first is released in tissues or plasma, and only later absorbed in red blood cells. The permeability of the red blood cell membrane to nitroprusside is low.[17] Smith and Kruszyna[5] incubated whole blood *in vitro* with high concentrations of nitroprusside (400 μM or 119 μg/ml), and one would expect that under these conditions the sulfhydryl groups in hemoglobin would remove cyanide after nitroprusside had diffused by mass action into the red blood cell. If the degradation *in vivo* proceeds similarly to that seen with photodegradation (fig. 5), it is possible that once the nitrosyl moiety has been removed, the further release of cyanide may be enhanced.

Potential Toxicity of Photoexposed Nitroprusside

The release of nitric oxide from the molecule during photodegradation preceded the release of cyanide (figs. 4 and 5), suggesting that for free cyanide to be released, the iron–nitrosyl coordination complex in the molecule first must be disrupted. With further degradation, the release of nitric oxide was linear, while that of cyanide increased exponentially. This suggests that as degradation progresses, the potential for toxicity from free cyanide in the infusate becomes more significant. Since photodegraded nitroprusside (containing liberated NO) had the same hypotensive effect as the intact molecule, one could argue from our data that solutions of nitroprusside used to induce short-term intraoperative hypotension do not need to be protected from light, especially if one assumes that both degraded and intact nitroprusside release the same amount of cyanide *in vivo*. However, in our experiments, nitroprusside was exposed to light under carefully controlled conditions. In contrast, the intensity of light incident on unprotected nitroprusside in the operating room environment is neither controlled nor monitored. Since the release of free cyanide from nitroprusside appeared to be a function of the combination of illuminance and duration of exposure, a short-term exposure of unprotected nitroprusside to operating room lights of high intensity has the potential to release a clinically significant amount of cyanide. For this reason, we feel that protection of nitroprusside is important. Protection should be carried out by wrapping the reservoir of nitroprusside with an opaque material as has been customary, although perhaps one might be able to substitute red glassware and tubing with satisfactory results (fig. 4).

Conclusions

We conclude the following: 1) Sodium nitroprusside is sensitive to white light and blue light, but it remains intact in red light. The photodegradation of nitroprusside is accompanied initially by the release of nitric oxide, followed subsequently by the release of cyanide. 2) The cyanide measured in blood from patients receiving nitroprusside is not an artifact of assay methods. 3) Degraded nitroprusside remains biologically active. 4) Degraded nitroprusside may be more toxic than intact nitroprusside, since free cyanide is a product of degradation. We find unambiguous evidence that cyanide is released from nitroprusside *in vivo*, and appropriate caution should continue to be exercised when using this drug.

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