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Carcinogenicity of N-nitrosoamines Derived from Reaction of Sodium Nitroprusside with Some Therapeutically Important Secondary Amines

To the Editor:—In a recent letter to the editor, Park and Means[1] pointed out the potential carcinogenic hazards of the use of the hypotensive agent sodium nitroprusside in patients also receiving drugs which contain a secondary amine functionality. This hazard was in the form of the sodium nitroprusside reacting, even under physiological conditions and concentrations, with the therapeutic amines to form potentially carcinogenic nitrosoamines. While some of the N-nitrosoamines which were shown to have been formed by this reaction have been previously tested by Lijinsky[2*] and found to be carcinogenic in at least the Sprague-Dawley rat model, the others in the list of Park and Means have not, to our knowledge, been tested at all.

Using an artificial intelligence program,[3] we were recently successful in classifying the carcinogenic potential of the 39 N-nitroso compounds tested by Lijinsky (37 out of 39 of the N-nitroso compounds were correctly classified as to carcinogenicity in a retrofit of the original data). Because of this and other successful uses of this program in the related area of mutagenicity,[4-7] your readers may be interested in the results of our prediction of potential carcinogenicity for the compounds listed in the letter of Park and Mean. The results are shown in table 1 (compounds 1–6).

The first three compounds in table 1, N-nitrosopiperazine, N,N-dinitrosopiperazine, and N-nitrosomorpholine are among the compounds that have been experimentally tested for carcinogenic activity. Of the remaining ones, only nitrosoephedrine is predicted to be carcinogenic. This is particularly significant because the drug from which it is derived, ephedrine, is readily available over the counter, and may be present in a patient's blood unbeknownst to the physician administering nitroprusside.

In view of the potential importance of Park and Mean's observations, we submitted to computer analysis another seven drugs often administered in conjunction with sodium nitroprusside (table 1, compounds 7 to 13), even though their transformation into N-nitrosoamines under physiological conditions has not yet been reported in the literature. Of the seven compounds analyzed, four are found to be suspicious and deserve further analysis. Fortunately, nifedipine, a calcium channel blocker that has often been used in conjunction with sodium nitroprusside, is not found to produce a carcinogenic N-nitrosoamine. However, its structure and that of a number of the other inactive compounds are significantly different from those of the original compounds upon which the predictions are based and, therefore, their predicted inactivity must be viewed with some caution.

TABLE 1. Secondary Amines, Their N-nitrosoamine Derivatives, and Their Actual and/or Calculated Carcinogenic Potential in Rats

Drug	N-nitroso Derivative(s)	Activity†	
		Actual	Calculated
Piperazine	N-nitrosopiperazine	++++	+++
	N,N-dinitrosopiperazine	—	+++
Morpholine	N-nitrosomorpholine	++++	++++
Ephedrine	N-nitrosoephedrine	?	++++
Ethambutol	N-nitrosoethambutol	?	—
	N,N-dinitrosoethambutol	?	—
Propranolol	N-nitrosopropanolol	?	—
Phentolamine	N-nitrosophentolamine	?	—
Chlorodiazepoxide	N-nitrosochlorodiazepoxide	?	++++
Epinephrine	N-nitrosoepinephrine	?	++++
Proline	N-nitrosoproline	?	—
Tetracaine	N-nitrosotetracaine	?	—
Ketamine	N-nitrosoketamine	?	+++
Methamphetamine	N-nitrosoamphetamine	?	+++
Nifedipine	N-nitrosonifedipine	?	—

† Actual activities are from Lijinsky,[2*] and calculated activities are from the CASE program. The following scale was used: ++++ = very active, +++ = moderately active, — = inactive, and ? = activity unknown.

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* The database was provided by Dr. W. Lijinsky, Chemical Carcinogenesis Program, Frederick Cancer Research Center, Frederick, MD 27101

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Preventing Ambient Light from Affecting Pulse Oximetry

To the Editor:—The photodetectors in flexible pulse oximeter probes are unable to discriminate between ambient light and the light produced by the light emitting diodes. The interference of ambient light—for example, surgical lights or heating lamps—with pulse oximetry monitoring in the operating room has been described.[1] One solution is to cover the probe site with some opaque material, such as a surgical towel. Although this approach is generally useful, with active neonates or restless patients, the towel frequently becomes displaced and exposes the oximeter probe.

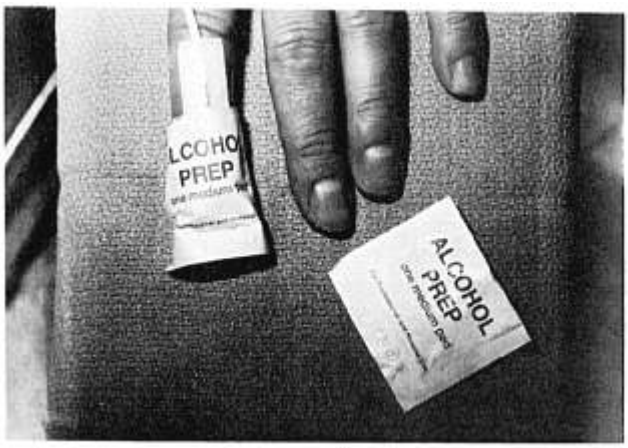

FIG. 1. A pulse oximeter probe is protected from ambient light by means of the packaging originally used for alcohol swabs.

We would like to describe a simple, effective remedy to this problem; that is, covering the probe, while it is attached to a digit, with the packaging from an alcohol swab. This packaging is lined with metallic foil and, thus, is opaque and malleable. Also, the packaging is manufactured in a shape that makes a convenient, dark receptacle for a digit, even one on which a flexible pulse oximeter probe has been placed (fig. 1).

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A Method of Securing the Stethoscope Head

To the Editor:—Few would deny that the oldest and simplest transducer used in anesthesiology, the precordial stethoscope, is still one of the best. Its only defect, in my experience, is its vulnerability to dislodgment by the efforts of the surgical team, despite many tricks to prevent this.

In prepubertal children where the musculature of the chest wall has not reached its adult development, an alternative site for the stethoscope head is in the left axilla where it is protected from such displacement. By trial and error, it is almost always possible to adequately hear both breath and heart sounds.