Antidotal Efficacy of Tetraethylenepentamine for Acute Nickel Carbonyl Poisoning in Rats [1]

D. C. JONES, P. M. MAY, D. R. WILLIAMS,

Department of Applied Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU, U.K.

M. C. REID and F. W. SUNDERMAN Jr.

Departments of Laboratory Medicine and Pharmacology, University of Connecticut School of Medicine, Farmington, Conn. 06032, U.S.A.

(Received November 3, 1983)

The development of chelating drugs for treatment of metal poisoning involves several interesting problems. For example, a chelating agent that mobilizes a certain metal ion from the intracellular to the extracellular compartments may not enhance the excretion of the metal ion from the extracellular fluid into the urine or feces. Secondly, low-molecular-weight exogenous ligands that serve as chelating drugs seldom provide absolute specificity for metal ion complexation *in vivo*; instead, such ligands typically form complexes with assorted metal ions. May and Williams [1] developed a computer technique for simulating chelation therapy; the technique generates Plasma Mobilization Index curves that are superior to Effective Stability Constants as predictors of *in vivo* chelation activity. The present report describes a practical application of the computer simulation technique; tetraethylenepentamine (TEP) was identified by its Plasma Mobilization Index curves as a promising agent for therapeutic complexation of Ni[II]. The prediction that TEP has antidotal efficacy in nickel poisoning was verified by a pilot trial in rats exposed to inhalation of nickel carbonyl, $Ni(CO)_4$.

As illustrated in Figs. 1 and 2, computer simulation studies, performed according to May and Williams [1], indicate that TEP is superior to triethylenetetramine (TRIEN) or N,N-bis(2-aminoethyl)1,3-propanediamine (ADP) as a Ni[II]-chelator, having a more powerful chelating effect and providing greater selectivity for Ni[II] in comparison to Cu[II] or Zn[II]. Since the toxicity of TEP in rats has not previously been tested, our next step was to assess the toxicity of TEP, itself. The acute toxicity of TEP was tested in 151 male Fischer-344 rats (body wt. = 175 to 300 g), distributed in 14 groups (9 - 12 rats/group). Recrystallized TEP·5HCl was dissolved in water, adjusted to pH 7.2–7.4 with Na_2CO_3 solution, and administered to rats by a single ip injection at 14 dosages ranging from 0.15 to 3.45 mmol/kg (body wt.). The acute mortality data (deaths within 2 weeks) were

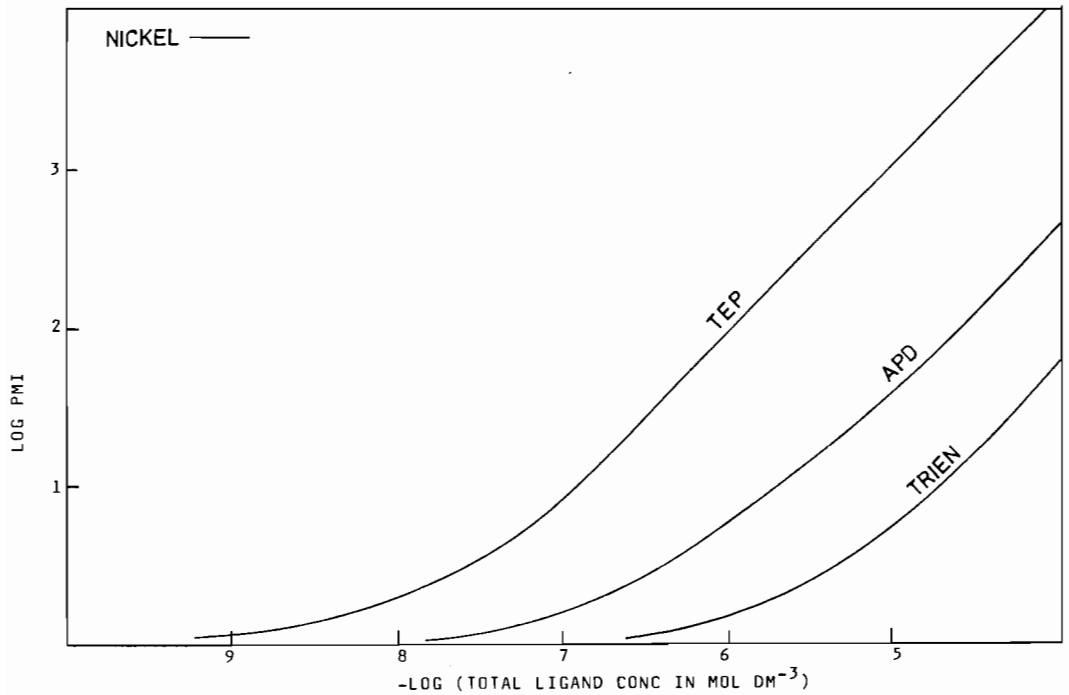

Fig. 1. Computer-generated curves for log of Ni[II] Plasma Mobilization Index (PMI) plotted *versus* –log of the concentrations of three drugs (TEP = tetraethylenepentamine; APD = N,N-bis(2-aminoethyl)1,3-propanediamine; TRIEN = triethylenetetramine). APD is a new agent which shows promise in having increased selectivity for copper [16].

0020-1693/84/$3.00

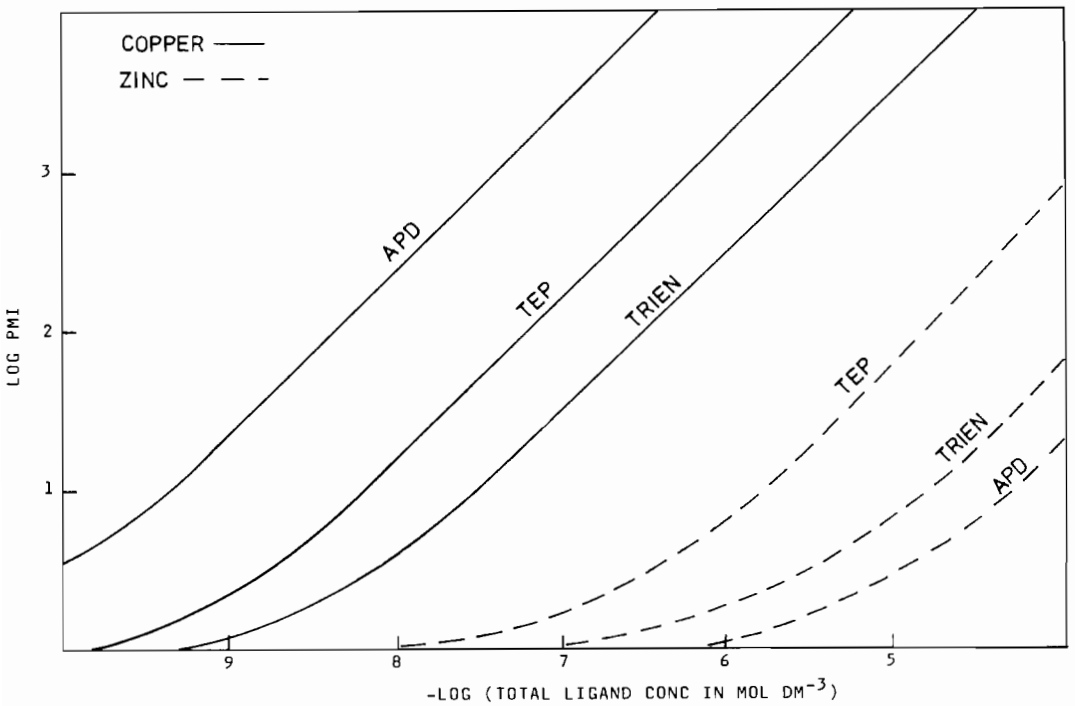

Fig. 2. Computer-generated curves for log of Cu[II] and Zn[II] Plasma Mobilization Indexes (PMI) plotted *versus* –log of the concentrations of three drugs (see legend to Fig. 1 for abbreviations).

TABLE I. Antidotal Efficacy of TEP and DDC, Singly or in Combination, in Male Fischer Rats Exposed to Inhalation of $Ni(CO)_4$.

Group	$Ni(CO)_4$ exposure (mg/L/ 15 min)	Drug	Dosages of drug[a] (mmol/kg)	Mortality ratio at two weeks	Interval between $Ni(CO)_4$ & death (days)[b]
A	1.6	Controls	0	9/9	<1 (<1–4)
B	1.6	DDC	4.1	3/9[c]	1
C	1.6	TEP	0.65	2/9[c]	2.5 (2,3)
D	1.6	DDC & TEP	4.1 (DDC) & 0.65 (TEP)	1/9[c]	>5

[a]The drugs were administered im (in dosages equivalent to 0.6 times their ip LD50 values) at 10 min prior to exposure to inhalation of $Ni(CO)_4$. [b]The values are medians and ranges. [c]$P < 0.01$ *versus* controls by Fisher's exact test.

used for computations of LD5, LD50, and LD95 doses by the method of Miller and Tainter (2), and the slope-function of the probit mortality curve was computed according to Litchfield and Wilcoxon [3]. The following mortality indices were obtained for TEP: LD5 = 0.78 mmol/kg; LD50 = 1.08 mmol/kg; LD95 = 1.90 mmol/kg; slope-function = 1.39. Our next step was to assess the antidotal efficacy of TEP for $Ni(CO)_4$ poisoning in rats. Four groups of 9 male Fischer rats were exposed to inhalation of a lethal atmospheric concentration of $Ni(CO)_4$, by the method of Baselt *et al.* [4]. As indicated in Table I, administration of sodium diethyldithiocarbamate (DDC) alone, TEP alone, or the combination of DDC and TEP, significantly reduced the mortality of rats following exposure to $Ni(CO)_4$; the antidotal efficacy of TEP was approximately equal to DDC in this pilot experiment; the data suggest that the combination of DDC and TEP might be synergistic. Further animal tests are underway to compare the therapeutic efficacies of DDC and TEP, singly and in various dosage combinations, in rats exposed to $Ni(CO)_4$. More research is required before firm conclusions can be reached, but the pilot study indicates that TEP may be a valuable addition to the roster of *in vivo* chelators for NI[II].

For discussions of chelation therapy for nickel poisoning, readers are referred to several recent articles [5–13]. DDC has proven to be more effective than disulfiram, d-penicillamine, or TRIEN as an

antidote for acute $Ni(CO)_4$ poisoning in rodents [4, 5]. $Ni(CO)_4$ is a volatile, lipid-soluble compound that readily penetrates the pulmonary alveolar wall, the blood-brain barrier, and cell membranes in target tissues [8, 10]. The therapeutic efficacy of DDC in $Ni(CO)_4$ poisoning apparently reflects the ability of DDC to form an intracellular Ni[II]-complex, with gradual release of the Ni[II]-complex into extracellular fluids [9, 10]. The therapeutic efficacy of TEP in $Ni(CO)_4$ poisoning seems likely to involve extracellular complexation of Ni[II] and enhanced renal clearance of Ni[II], as previously reported for TRIEN [8, 14, 15]. Therefore, the authors speculate that DDC and TEP may act synergistically, based upon the premise the DDC mobilizes nickel from the intracellular to the extracellular compartment in $Ni(CO)_4$-treated rats, and that TEP takes over from DDC, forming a charged Ni[II]-complex that is preferentially excreted in urine.

References

1 P. M. May and D. R. Williams, *FEBS Lett., 78,* 134 (1977).
2 L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med., 57,* 261–264 (1944).
3 J. T. Litchfield, Jr. and F. Wilcoxon, *J. Pharmacol., 96,* 99 (1949).
4 R. C. Baselt, F. W. Sunderman Jr., J. Mitchell and E. Horak, *Res. Commun. Chem. Pathol. Pharmacol., 18,* 677 (1977).
5 R. C. Baselt and V. W. Hanson, *Res. Commun. Chem. Pathol. Pharmacol., 38,* 113 (1982).
6 E. Horak, F. W. Sunderman Jr. and B. Sarkar, *Res. Commun. Chem. Pathol. Pharmacol., 14,* 153 (1976).
7 M. M. Jones, M. A. Basinger and A. D. Weaver, *J. Inorg. Nucl. Chem., 43,* 1705 (1981).
8 A. Oskarsson and H. Tjalve, *Acta Pharmacol. Toxicol., 41* (Suppl. 1), 158 (1977).
9 A. Oskarsson and H. Tjalve, *Arch. Toxicol., 45,* 45 (1980).
10 S. K. Shen, S. Williams, C. Onkelinx and F. W. Sunderman, Jr., *Toxicol. Appl. Pharmacol., 51,* 209 (1979).
11 F. W. Sunderman Sr., *Ann. Clin. Lab. Sci., 9,* 1 (1979).
12 F. W. Sunderman Sr., *Ann. Clin. Lab. Sci., 11,* 1 (1981).
13 S. K. Tandon and R. C. Srivastava, 'Nickel in the Environment', J. O. Nriagu, John Wiley and Sons, New York, pp. 569–583 (1980).
14 R. S. Dwivedi, G. Kaur, S. K. Hasan and R. C. Srivastava, *Chemosphere, 11,* 925 (1978).
15 F. W. Sunderman Jr., K. S. Kasprzak, E. Horak, P. Gitlitz and C. Onkelinx, *Toxicol. Appl. Pharmacol., 38,* 177 (1976).
16 P. M. May, D. C. Jones and D. R. Williams, *The Lancet,* May, 1127 and July, 273 (1982).