The Geographic Distribution of Tuberculosis and Pyridoxine Supply in Ontario

Michael A. McGuigan and Janet Yamada

ABSTRACT

Acute poisoning with isoniazid causes generalized convulsions which should be treated with intravenous pyridoxine and a rapidly-acting anticonvulsant. The purpose of this study was to determine the correlation between the distribution of tuberculosis (as a proxy for isoniazid use) and acute care hospital supplies of intravenous pyridoxine (the antidote for isoniazid overdose). The distribution of tuberculosis was based on Ontario public health regions. The study was descriptive using simple linear regression to assess the degree of correlation.

Only 15.6% of Ontario acute care hospitals have enough intravenous pyridoxine to treat an average isoniazid overdose. The distribution of tuberculosis and the number of hospitals in the region correlated best with hospital supplies of pyridoxine, although these variables explained only 22% and 23.7%, respectively, of the variation in supply.

It does not appear that the distribution of tuberculosis is a major determinant of the availability of the isoniazid antidote, pyridoxine. Acute care hospitals in Ontario should re-evaluate their need for pyridoxine in light of the incidence of tuberculosis in their regions. Each hospital should stock at least 5 Gm of intravenous pyridoxine; additional amounts may be appropriate if there is an increased incidence in the area.

Key Words: *isoniazid, overdose, pyridoxine, tuberculosis.*

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RÉSUMÉ

L'intoxication aiguë à l'isoniazide provoque des convulsions généralisées qui devraient être traitées par l'administration de pyridoxine intraveineuse et d'un anticonvulsivant à action rapide. Le but de cette étude était de déterminer la corrélation entre les distributions de la tuberculose (comme variable subrogative de l'usage de l'isoniazide) et les stocks de pyridoxine intraveineuse (l'antidote au surdosage d'isoniazide) des hôpitaux de soins de courte durée. La distribution de la tuberculose était basée sur des régions de santé publique de l'Ontario. Cette étude descriptive faisait appel à une méthode de régression linéaire simple permettant d'évaluer le degré de corrélation.

Seulement 15,6 % des hôpitaux ontariens de soins de courte durée ont suffisamment de pyridoxine intraveineuse pour traiter un surdosage moyen d'isoniazide. La distribution de la tuberculose et le nombre d'hôpitaux de la région présentaient la plus forte corrélation avec les stocks hospitaliers de pyridoxine, bien que ces variables n'aient pu expliquer que 22 et 23,7 %, respectivement, de la variation des stocks.

Il ne semble pas que la distribution de la tuberculose constitue un facteur déterminant important de la disponibilité de l'antidote de l'isoniazide, la pyridoxine. Les hôpitaux ontariens de soins de courte durée devraient réévaluer leurs besoins en pyridoxine en fonction de l'incidence de la tuberculose dans leurs régions. Chaque hôpital devrait avoir en stock au moins 5 g de pyridoxine intraveineuse; des quantités supplémentaires pourraient être utiles si l'incidence de la tuberculose était plus élevée dans une région particulière.

Mots clés : *isoniazide, pyridoxine, surdosage, tuberculose.*

INTRODUCTION

Isoniazid is widely used for the prophylaxis and treatment of tuberculosis, and isoniazid overdose tends to occur in populations with a high incidence of tuberculosis.[1-3] Isoniazid administration inactivates pyridoxine, a cofactor necessary for the production of the inhibitory neurotransmitter gamma-amino-butyric acid (GABA). The acute ingestion of more than 35 mg of isoniazid per kilogram body weight is considered to be toxic and more than 70 mg/kg is potentially fatal. Following isoniazid overdose, acutely reduced central nervous system levels of GABA can result in uncontrolled convulsions. Generalized convulsions, coma, and metabolic (lactic) acidosis occur within two hours of the ingestion. One of the important aspects of isoniazid overdose is the rapid development of convulsions that are resistant to

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treatment with standard anticonvulsant medications.[4] However, the intravenous administration of pyridoxine is a specific and effective treatment for isoniazid-induced convulsions. The current recommendations for treating isoniazid-induced convulsions are to administer intravenously an amount of pyridoxine equal to the amount of isoniazid ingested.[5,6] For ingestions of unknown quantities of isoniazid, it is recommended that the patient receive an initial dose of 5 grams of pyridoxine.[5,6] Although unsubstantiated, it has been claimed that earlier treatment with pyridoxine is associated with fewer complications.[7] All pyridoxine doses should be given in conjunction with a rapidly acting anticonvulsant drug (e.g., a benzodiazepine).[8] Anticonvulsants alone are not sufficient to stop isoniazid-induced convulsions. Animal experiments have documented that phenobarbital or phenytoin is not effective in controlling convulsions unless the drug is given in conjunction with pyridoxine.[4] Similarly, the administration of diazepam alone has resulted in incomplete treatment of isoniazid poisoning in animals;[8] other benzodiazepines have not been evaluated. For these reasons, it is necessary for an acute care hospital to have adequate stocks of pyridoxine on site.

While acute isoniazid overdoses are not common (only 453 cases were reported for 1993 by the American Association of Poison Control Centers), the outcome may be serious. Of the 311 cases for which outcome data were reported, 65 patients (20.9%) developed moderate toxicity (significant but not life-threatening effects that responded quickly to treatment), 59 patients (19%) experienced major toxicity (effects that were life-threatening or resulted in significant residual disability), and two patients (0.64%) died.[9] Because of the dangers of overdose associated with isoniazid use, an appropriate supply of pyridoxine should be present in each acute care hospital that serves a population with a high incidence of tuberculosis. The purpose of this study was to evaluate and compare the geographic distribution of tuberculosis cases and the supplies of pyridoxine in acute care hospitals in Ontario.

METHODS

Tuberculosis is a "reportable" disease in Ontario. All active cases should be reported to the Public Health Branch of the Ontario Ministry of Health. The geographic distributon of tuberculosis cases during the period 1989-1992 were reported by the Public Health Branch as the number of cases occurring in each of the 42 public health units or regions.[10] Current (1994) hospital supplies of intravenous pyridoxine were obtained by a telephone survey of Ontario hospital pharmacies during which it was confirmed that the hospital offered emergency services. Only hospitals with emergency departments were included in the survey because it was assumed that patients with overdoses or convulsions would go to those hospitals. Total supplies of pyridoxine in the health units were used in all analyses except when individual hospitals were considered. Hospital size (number of beds) was obtained from the Canadian Hospital Directory.[11] Reports of cases of isoniazid overdoses were obtained from 1989-1992 call records of the Ontario Regional Poison Centres in Ottawa and Toronto.

The data were categorized by public health unit.[12] Frequency distribution and simple linear regression to assess correlations were carried out using a commercial statistical software package (StatView II by ASBACUS CONCEPTS ©1987). Simple linear regression was performed on the following pairs: regional pyridoxine supply vs. regional number of tuberculosis cases, regional pyridoxine supply vs. regional number of hospitals, regional pyridoxine supply vs. regional population; and individual hospital supply of pyridoxine vs. individual hospital size. In each analysis, the supply of pyridoxine was considered the "dependent" variable. The coefficient of determination (r^2) was chosen as the outcome measure because it is an indicator of how much of the variation in one variable is due to variation in another variable.

RESULTS

The average number of tuberculosis cases reported by the health units for the years 1989-1992 ranged from 1-179.5 cases. The geographic distribution of tuberculosis cases in Ontario[10] is shown in Figure 1. One hundred and eighty-seven acute care hospitals were identified. The reported

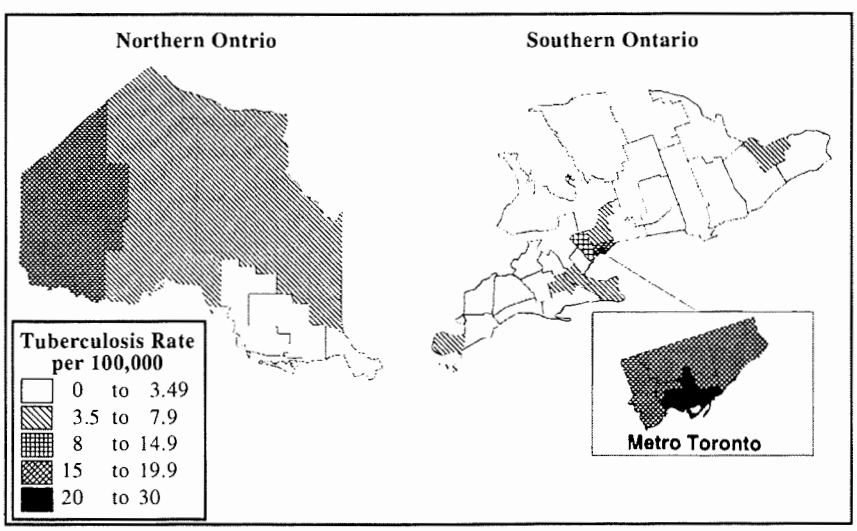

Figure 1. Tuberculosis Average Annual Incidence by Health Unit, Ontario 1989-1992

hospital supplies of pyridoxine by health unit ranged from 0-48 Gm. The geographic distribution of pyridoxine was highly variable. Although all of the correlations were poor, the two best were the supply of pyridoxine with the number of tuberculosis cases in the region ($r^2 = 0.220$, $p = 0.002$) (Figure 2), and the supply of pyridoxine with the number of hospitals in the region ($r^2 = 0.237$, $p = 0.001$) (Figure 3). The correlation between pyridoxine supplies and the individual hospital size was low ($r^2 = 0.082$, $p = 0.0001$) (Figure 4). The correlation between the population in the health unit and the supply of pyridoxine also was low ($r^2 = 0.187$, $p = 0.004$) (Figure 5).

To eliminate the influence of outlier data points, the coefficients of determination were recalculated with the outliers omitted. In each case, the r^2 value was reduced: for Figure 2, $r^2 = 0.001$ ($p = 0.87$); for Figure 3, $r^2 = 0.145$ ($p = 0.014$); for Figure 4, $r^2 = 0.022$ ($p = 0.039$); and for Figure 5, $r^2 = 0.091$ ($p = 0.055$).

The frequency distribution of "therapeutic" (≥5 Gm) supplies of pyridoxine was analyzed. Only 15.6% of hospitals had ≥5 Gm of pyridoxine (enough to treat an "average" adult overdose of 5 Gm of isoniazid). Approximately 66.7% of the hospitals had no pyridoxine and the rest (17.7%) had potentially inadequate supplies of pyridoxine.

A review of Ontario Regional Poison Centre call data revealed only three cases of isoniazid overdose during the study period (one of which developed convulsions). None of the cases were reported from a hospital that currently has adequate pyridoxine supplies.

DISCUSSION

The analysis presented in this paper attempts to link public health data (distribution and incidence of tuberculosis) with clinical toxicology (supply of pyridoxine). It is reasonable to expect that a specific antidote will be available in areas where the risk of exposure to a particular toxin is significant. Analysis of the data demon-

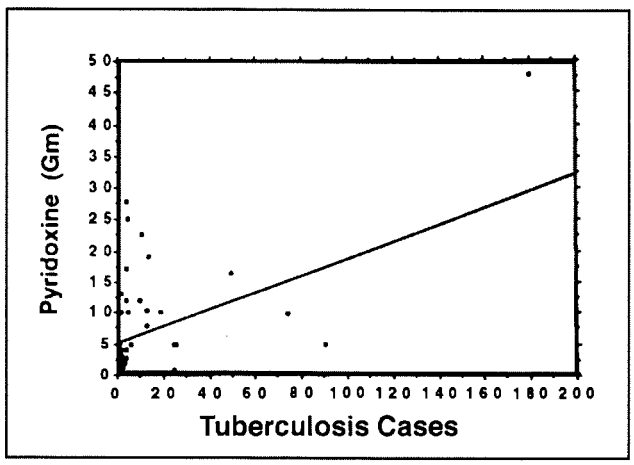

Figure 2. Regional Number of Tuberculosis Cases vs Pyridoxine Supply ($r^2 = 0.220$)

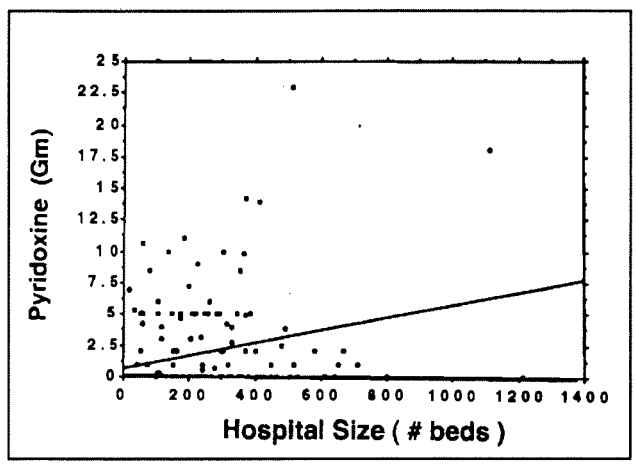

Figure 4. Individual Hospital Size vs Pyridoxine Supply ($r^2 = 0.080$)

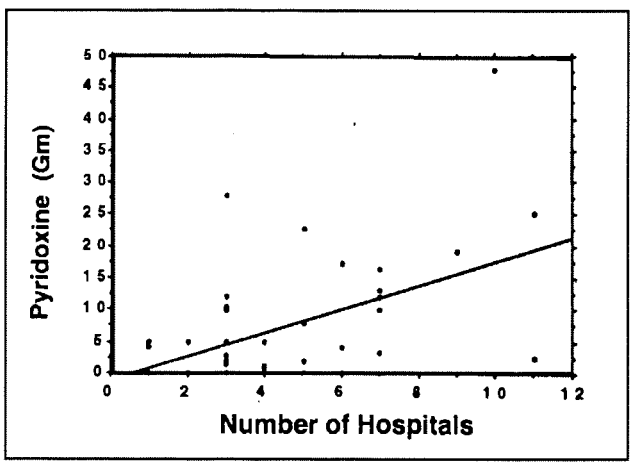

Figure 3. Regional Number of Hospitals vs Regional Pyridoxine Supply ($r^2 = 0.240$)

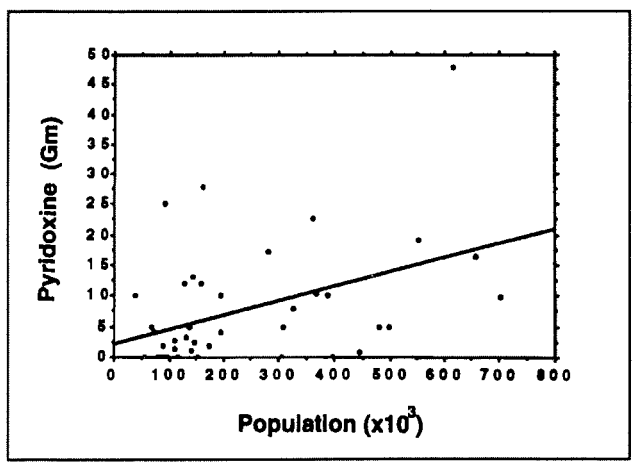

Figure 5. Regional Population vs Regional Pyridoxine Supply ($r^2 = 0.190$)

strated that this is not the case. The relationship between the distribution of pyridoxine supplies and the geographic distribution of reported tuberculosis cases has an r^2 of 0.220. This means that the number of tuberculosis cases in a health region accounts for only 22% of the observed variation in pyridoxine supplies. The possibility always exists that there are other meaningful variables that have not been included in the analysis. A coefficient of determination of 0.220 suggests that the supplies of pyridoxine in public health regions depend to a large degree on factors other than the number of tuberculosis cases in that region. Other influences on the supplies of pyridoxine analyzed were the number of hospitals in a health unit region (r^2 = 0.237), the population of the health region (r^2=0.187), and hospital size (r^2=0.082).

Other factors must be considered when interpreting these results. Public health unit aggregate distribution data may not accurately reflect the micro-distribution of tuberculosis within a health unit. It is possible that within a public health unit, individual hospitals that see more tuberculosis cases may have appropriate supplies of pyridoxine. This analysis was not possible to do with available public health data. Ideally, the distribution and number of people on isoniazid should have been used. Alternatively, the amount of isoniazid dispensed by hospital or community pharmacies in each health unit also could have been used. Since neither of these pieces of information were available, active cases of tuberculosis were used as a proxy for isoniazid use. Using active cases of tuberculosis may overestimate isoniazid use because some cases of active tuberculosis may be treated with drugs other than isoniazid. On the other hand, the use of isoniazid may be considerably larger than estimations based on active cases because it is recommended that test-positive tuberculosis contacts also be treated with isoniazid.[13] However, it is possible that test-positive individuals have a significantly different public health unit distribution than people being treated for active disease. Finally, the comparison of 1989-92 disease incidence with 1994 pyridoxine supplies may introduce inaccuracies if either the disease incidence or the pyridoxine supplies changed significantly in the period from 1992 to 1994.

The number of isoniazid overdoses reported by the Ontario Regional Poison Centres was very small compared to the probable number of people using isoniazid. This may represent safe use of isoniazid by the public or under-reporting to the Poison Centres. Contacting a Poison Centre is voluntary so it is possible that the Poison Centre call data did not capture all of the cases of isoniazid overdose.

In conclusion, the overall morbidity and mortality associated with inappropriately treated isoniazid overdoses is likely to be low but has not been established. The fact remains that isoniazid is a potentially dangerous drug and intentional or accidental overdoses will occur. Acute care hospitals in Ontario should re-evaluate their need for pyridoxine in light of the incidence of tuberculosis in their regions. The assumption of a linear correlation between pyridoxine supplies and incidence of tuberculosis suggests that each hospital should have at least 5 Gm of pyridoxine on site and that the amounts should increase with the tuberculosis incidence. However, without a formal pharmacoeconomic analysis of the issues raised by this study, more specific recommendations would be inappropriate.

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