An Examination of Methemoglobinemia in Washington State

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Executive Summary

Nitrate contamination of groundwater used for drinking water supplies can cause adverse health effects. Some health effects are only suspected. However, it is known that methemoglobinemia ("blue baby syndrome") is associated with the ingestion of nitrate contaminated water by infants. Methemoglobinemia is not a reportable condition. It is very rare and little is known about its prevalence in Washington. This study attempts to examine the prevalence of methemoglobinemia.

Health care providers currently licensed to practice in counties with the Columbia Basin were surveyed. Hospital discharge (CHARS) data for the period of 1988-1994 were reviewed for cases of methemolglobinemia across Washington State.

The overall response rate to the health care provider survey was 75% (n=91). Ninety-four percent of the respondents *did not* report a confirmed or suspected case of methemoglobinemia within the past five years. Seven cases were reported by physicians located in Benton and Lincoln counties.

Cases of methemoglobinemia were also identified using the hospital discharge data in Clark, Island, King, Pierce, Spokane, and Yakima counties over a five-year period. Five cases were reported in Spokane county over a three-year period ('90 - '92).

Even though cases were identified from these two separate data sources, biases are inherent in both sources and none of the cases were linked with the ingestion of nitrates. However, this work is an initial effort to define the scope and magnitude of health effects associated with nitrates in Washington.

Introduction

The Washington State Departments of Health (DOH), Ecology, and Agriculture, the Washington Conservation Commission, and the U.S. Environmental Protection Agency (EPA) met to discuss the issue of nitrate contamination of the groundwater in the Central Columbia Plateau of eastern Washington in the spring of 1995. As a result of this discussion, they requested the Interagency Ground Water Committee (IGWC)[1] recommend a strategy to address:

- Extent and magnitude of the nitrate problem.
- Identification of populations at risk of health effects from nitrate ingestion.
- Dissemination of information to the public and risk communication.
- Short-term and long-term remediation.
- Integration and cooperation with federa , state, local, and tribal agencies in regard to nitrate issues.

The United States Geological Service (USGS), in their recent publication *Nitrate Concentrations in Ground Water of the Central Columbia Plateau* (Open-File Report 95-445, S.J. Ryker and J.L. Jones, October 1995), found that 19% of 573 wells tested for nitrate in the Central Columbia Plateau exceeded the EPA maximum contaminant level (MCL) of 10 parts per million for drinking water.

From a public health standpoint, nitrate contamination of groundwater used for drinking water supplies can cause adverse health effects. Some health effects are only suspected. However, it is known that methemoglobinemia ("blue baby syndrome") is associated with the ingestion of nitrate contaminated water by infants. The National Academy of Sciences concluded that approximately 10 mg/l as nitrogen (45 ppm nitrate) is the maximum concentration of nitrates in water with no observed adverse health effects (based on methemoglobinemia as the endpoint health effect). (National Research Council, 1995) Since the concentration of nitrates in 19% of the wells tested in the Central Columbia Basin exceeded the 10 mg/l maximum allowable level (MCL), considerable concern has been expressed about the potential for an excess risk of methemoglobinemia among the residents of this region. Methemoglobinemia is not a reportable condition. It is a very rare condition and little is known about its prevalence

[1] The Interagency Ground Water Committee (IGWC) was formed in January 1992 and is comprised of representatives from federal, state, local and tribal governments and public groups. Its primary goal is to protect and preserve the groundwaters of Washington State. The IGWC does not render policy decisions. It serves as a clearinghouse for ground water issues, policies, and action on a interagency, intergovernmental basis, so that groundwater issues may be dealt with in a more comprehensive manner. The IGWC can make recommendations on the most effective ways to deal with a groundwater issue. These recommendations are referred to the appropriate governmental agency(ies) for policy development and implementation.

- To examine the prevalence of methemoglobinemia among children in counties within the Central Columbia Plateau through surveying selected health care providers working in these counties about their recall of cases over the past five years.

- To determine the demographic characteristics and the geographic distribution in Washington of cases of methemoglobinemia among children reported in the Comprehensive Hospital Abstract Reporting System (CHARS) for the years 1988 - 1994.

References

National Academy of Sciences--*Nitrate and Nitrite in Drinking Water,* Subcommittee on Nitrate and Nitrite in Drinking Water, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences National Research Council. National Academy of Sciences, Washington, D.C., 1995.

Background

Harriet M. Ammann, Ph.D., D.A.B.T. [2 3]

Nitrogen is essential to the maintenance of human health, primarily as a constituent of amino acids and protein in consumed food. This essential element is recycled through reactions occurring in soil bacteria, plants, and animals. According to recent studies, farmers apply 24-38% more nitrogen-containing fertilizers than crops require due to uncertainties associated with soil nutrient studies and weather [Puckett(1)]. Excess nitrate can percolate into aquifers and contaminate drinking water. Shallow wells are particularly prone to contamination from surface pollutants, including nitrate. The finding of high nitrate levels is often an indicator of other contaminants, including bacteria. Seepage of liquid effluent from holding pens or barns, or manure piles, as well as percolation from fields in which animals graze can contribute not only nitrate, but also bacterial contamination to groundwater. Shallow dug wells located close to such sources or to septic tanks have been identified as major sources of nitrate in drinking water [Bouchard et al.(2); Johnson and Kross(3); Craun et al.(4); Kross et al.(5)]. Many states have found that private shallow wells impacted by agriculture have nitrate levels above the MCL. The Iowa State-Wide Rural Well-Water Survey found 18% of private wells were above the MCL [Hallberg et al.(6)]. Of 1,000 wells surveyed in Big Sioux River Basin, South Dakota, 27% had nitrate levels above the MCL [Meyer (7)]. South Dakota physicians surveyed about their recall of methemoglobinemia cases in these regions where high nitrate levels were found in wells reported 80 cases [Goodman(8)].

There is a natural variation in susceptibility to the toxicity of nitrate among adults and infants. Individual susceptibility is affected by the biochemical and physiologic characteristics of the individual. When the concentration of met hemoglobin (metHb) is greater than 10% of total hemoglobin (Hb), clinical signs of anoxia develop. The enzyme methemoglobin reductase is able to reduce met hemoglobin back to normal hemoglobin.

Infants have specific susceptibilities, however, which most adults do not have. Young infants (less than 4 months of age) normally have only half the reductase enzyme activity of adults [ATSDR (9)]. Additionally, infants consume 3 times more water relative to their body weight than adults do, and thus have a higher exposure to nitrate when drinking formula made with contaminated water [Craun et al.(4)]. Several factors cause infants to have greater susceptibility to nitrate exposure. A large proportion of Hb in infants is in the form of fetal hemoglobin, which is more readily oxidized to metHb than adult hemoglobin is. The pH of the stomach is higher (more

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[3]Presented in part at the 8th Northwest On-Site Conference, University of Washington, Seattle, Washington, September 18-19, 1995

alkaline) in infants (about pH 3-4.5) than in adults (pH 1-2). [Walton(10)]. Above pH 4, bacteria which convert nitrate to nitrite can grow abundantly in the stomach, enhancing the absorption of nitrite. Gastroenteritis with vomiting and diarrhea enhances nitrite formation because of the resulting pH changes throughout the gut. While all four factors make young infants more susceptible to nitrate toxicity, infants with gastrointestinal problems are most at risk. In addition to the complications such illness produces in the form of dehydration, inflammation of the gastrointestinal mucosa can enhance nitrite absorption.

The signs of methemoglobinemia in infants are the development of a "dusky" or bluish color, especially around the mouth, hands and feet; lethargy, sweating, warm, flushed skin; vomiting and diarrhea; dehydration from vomiting and diarrhea. Drawn blood may have a chocolate brown color. These are all immediate symptoms from short-term exposure. Additionally there may be other effects such as failure to thrive, and physical or mental retardation, if exposure continues over time, due to the effects of oxygen deprivation, especially to the brain. Infants in poor nutritional status, or in whom symptoms of anoxia are not readily apparent, and who have gastrointestinal illness, may be at increased risk of not being diagnosed with methemoglobinemia.

The changes in skin color can be missed, especially in dark-skinned individuals. Poorly nourished infants, or infants with gastrointestinal illness, may display the other relatively nonspecific signs. Death of infants with higher exposures may be misdiagnosed as congenital heart disease, which displays similar signs, or sudden infant death syndrome (SIDS).

The toxicity of nitrate, especially as it applies to infants under 4 months of age, needs to be addressed in order to examine whether in fact such an allowable level in drinking water used for preparing baby formula is protective of the most sensitive population. Investigations leading to knowledge about and correction for water contamination is essential for prevention of nitrate caused illness in infants. Enhancement of physician awareness of the potential for methemoglobinemia can lead to early recognition and treatment of the condition. Tracking of illness, perhaps by including this condition as a reportable illness, may also raise physicians' awareness, and provide impetus for preventive measures. More conservative use of nitrogen containing fertilizer, and better on-site treatment for wastes, can be cost effective means for prevention of nitrate toxicity.

Methemoglobinemia associated with an environmental exposure is difficult to recognize or diagnose without an exposure history implicating nitrate. Further, methemoglobinemia ("blue baby syndrome") is not a reportable condition. These factors make it difficult to track illness case from health records, or to conduct surveys of health practitioners about their experiences with the illness. It is presently not known whether the large number of private wells with high nitrate levels found in recent investigations have resulted in cases of methemoglobinemia in young infants. Absence of evidence is not evidence of absence, however.

The U.S. EPA has established a maximum contaminant level (MCL) for the sum total of nitrate and nitrite in drinking water not to exceed 10 mg/l. Nitrate alone is not to exceed 10 mg/l, while nitrite alone is not to exceed 1 mg/l. Both compounds are to be measured as nitrogen [U.S. EPA (11)]. The MCL based on methemoglobinemia which is meant to protect normal infants, does not have a margin of safety. It may be at the *effect* level for infants with gastrointestinal illness.

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Methods

The first part of this study consisted of active epidemiologic surveillance. Health care providers were surveyed who were licensed to practice in counties within the Columbia Basin. A list of names and addresses was obtained from the Office of Licensing of the Washington State Department of Health. A sample of health care providers were selected for this survey who met the following criteria: 1) business address located in a county within the Central Columbia Basin (Adam, Benton, Douglas, Franklin, Grant and Lincoln); and 2) physicians specializing in obstetrics and gynecology, family practice and pediatrics; nurse practitioners and midwives. Registered nurses were not included because this professional group was quite large and would have quickly exhausted allocated resources, i.e., time and money. The questionnaire (Appendix A) inquired about the provider's knowledge of (1) suspected or confirmed cases of methemoglobinemia occurring in his/her community within the past five years; (2) the community's awareness of the causal relationship between nitrate ingestion and methemoglobinemia; and (3) the source of their patients' drinking water. It was mailed as a part of a packet of educational materials which also included two Department of Health fact sheet on nitrates and the *ATSDR Case Studies in Environmental Medicine: Nitrate Toxicity*. The survey was used as an opportunity to provide the health care providers with more information about nitrates and associated health effects. The initial mailing of the questionnaire was followed with postcard as a reminder one week later. The questionnaire and another letter were sent to all nonrespondents ten days after the postcards were mailed.

The second part of the study consisted of a passive surveillance project using CHARS data to identify cases of methemoglobinemia. The Washington State CHARS is designed to provide data which can be used to make a more accurate assessment of the health status of Washington residents. Data is collected on inpatients from all state-licensed acute care facilities in the state. Data are not collected from federal hospitals, freestanding clinics, outpatient/ambulatory care facilities nor hospitalizations of Washington residents outside the state. CHARS data for the period 1988 - 1994 were reviewed using the International Classification of Disease (ICD) code for methemoglobinemia - 289.7. CHARS data were examined for all Washington counties. Up to five diagnosis codes are reported for a each hospitalization. The first diagnosis code lists the condition that the patient was hospitalized with. The other four codes may indicate an illness that was present at the time of hospitalization though at a lesser severity than the one listed as the first diagnosis code, an illness that was not the immediate cause of the hospitalization, or a iatrogenic/nosocomial condition. If any of the five diagnosis were coded as methemoglobinemia, it was counted as a case. Among the information listed in this data system for each hospitalization were age, gender, zip code of residence, and county of residence. Unique identifiers are listed for each patient though the patient's anonymity is maintained.

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Personal communication with Vicki Hohner, Office of Hospital and Patient Data Systems, Washington State Department of Health, 1996.

Results

Active Surveillance

During July and August 1995, a questionnaire was mailed to 121 health care providers who practiced in counties within the Columbia Basin. These counties were Adams, Benton, Douglas, Franklin, Grant, and Lincoln. The overall response rate to the survey was 75% (n=91). By occupational group, the response rate for physicians was 74% (n=75); nurse practitioners and midwives 80% (n=20). The response rates by county are listed in Table 1. Forty-nine percent of the respondents have practiced in their respective geographical area for five years or more and 34.5% for at least one year or more. Reports of suspected and confirmed cases of methemoglobinemia are shown in Table 2. Ninety-four percent of the respondents *did not* report a confirmed or suspected case of methemoglobinemia within the past five years. Cases were reported by physicians located in Benton and Lincoln counties. Ninety-three percent of the respondents reported that their patients were not aware of the association between methemoglobinemia and nitrates. The source of drinking water as reported by the health care providers about their patients is shown in Table 3. Seventy-six percent reported that their patient's drinking water was from a community water supply.

Passive Surveillance

The age and distribution of the cases located in CHARS are presented in Table 4. Among the cases (n=13), ages 0 - 4 years, males constituted 61.5%. Cases of methemoglobinemia in children, ages 0 - 4 years were located in Clark, Island, King, Pierce, Spokane, and Yakima counties (Appendix B). Five cases were reported in Spokane county over a three year period ('90 - '92).

Table 1 Response Rates by County		
County	Number Mailed	Response Rate (%)
Adams	2	50
Benton	50	72
Douglas	9	89
Franklin	21	76
Grant	33	76
Lincoln	6	33
Total	121	75

Table 2 Suspected or Confirmed Cases of Methemoglobinemia Reported by Health Care Providers by County		
County	Past year	Past five years
Adams	0	0
Benton	1	6
Douglas	0	0
Franklin	0	0
Grant	0	0
Lincoln	0	1
Total	1	7

Table 3 Question: What is the source of drinking water for the majority of your patients?	
Single family wells	1.2% (1)
Community water supplies	76.2% (64)
Bottled water	13.1% (11)
Combination of Single family wells and Bottled Water	1.2% (1)
Combination of Single family wells and Community water supplies	8.3% (7)

Note: No diagnosis codes for cases of methemoglobinemia in 1989 listed.
* Age 0 indicates child less than one year old.

Table 4
Childhood Cases of Methemoglobinemia from CHARS

Year	County	Zip Code of Residence	Age (years)*	Gender	First Diagnosis
1988	Island	98277	0	F	Yes
1988	King	98112	0	M	No
1988	King	98277	0	M	No
1990	Spokane	99206	0	F	No
1990	Spokane	99207	0	M	Yes
1991	Yakima	98948	0	F	No
1991	Spokane	99205	0	F	Yes
1991	Spokane	99207	0	M	Yes
1992	Spokane	99206	0	F	Yes
1993	Pierce	98407	0	M	Yes
1993	Clark	98661	1	M	No
1993	Clark	98661	3	M	No
1994	Clark	98665	1	M	No

Discussion

Methemoglobinemia is a rare health condition. Only a few cases were reported by the survey respondents or identified in CHARS. A total of seven cases were reported by the survey respondents. The accuracy of the recall of these respondents might be suspect in most instances. Since methemoglobinemia is so rare, however, a provider who diagnosed or treated a case would most likely remember it. Of the seven cases reported, six cases were reported by one health care provider in Benton county. None of the cases reported by the health care providers within the Central Columbia Basin appeared in the CHARS system. The most likely explanation for this inconsistency is that the cases reported by the providers were not hospitalized. In accordance with the scope of this study as defined by the Washington State Department of Health/Department of Social and Human Services, Human Research Review Board, investigators did not contact providers to obtain more information about cases.

Health care providers practicing in counties outside of the Central Columbia Basin were not surveyed. However, cases of methemoglobinemia in children were founded in the CHARS system in these counties. The cases that were found in CHARS appeared to be clustered geographically in a few areas of the state. Clustering, defined as more than one case of methemoglobinemia in a single year, was seen in Spokane, King and Clark counties. In Spokane and Clark counties, cases were also reported over multiple years. Cases in which the first diagnosis code was methemoglobinemia were reported from Spokane, Island and Pierce counties. Age is an important factor in the development of environmentally-associated methemoglobinemia and most often affects children less than six months of age. Of the twelve cases of methemoglobinemia found, ten cases were in children less than a year old. Since methemoglobinemia can be caused by medical treatment, it is important to examine cases that reportedly had the condition upon hospital admission when attempting to identify environmentally-related cases. Cases were found which suggested a possible association with an environmental exposure in areas of the state with high nitrates in the water. This is purely *speculative* because this epidemiological study is ecological and known risk factors cannot be controlled. Without a review of the patient's medical records, the etiology of the cases of methemoglobinemia is unclear.

Questionnaires were sent to health care providers in one region of the state with not only potentially hazardous levels of nitrates in the groundwater but also a large number of private, shallow wells. Concern has been expressed that these private wells, due to their construction, are particularly prone to contamination with nitrates from agricultural runoff. Further, health officials have expressed concern about the lack of testing of private wells to identify the presence of contaminants, including nitrates. Seventy-six percent of the respondents reported that their patients were using community (public) water supplies for drinking water. For those patients on public water systems, nitrates may continue to be a problem. These water systems can be very small providing service to as few as three families, and a number of community

water systems in the state are out of compliance in regard to nitrates. The only assurance that their drinking water is nitrate free is to have it tested

Cases of methemoglobinemia were not found in the CHARS system for the Central Columbia basin. This is an area of the state considered at "high risk" based on known groundwater contamination. A total of seven cases were reported by health care providers in two counties over a five-year period. Not finding cases in high risk areas may, as previously stated, be indicative of few hospitalizations or it may demonstrate the effectiveness of a public health education program in the community. However, this "public health education" assumption contradicts the results of the health care provider survey. Only 7% of the respondents felt that their patients were cognizant of the health effects associated with nitrate exposure. Since some residents were reported using bottled water, they are apparently taking steps to limit their exposure to contaminants in drinking water.

Conclusion

In this study, tracking cases of methemoglobinemia in this state was initiated. Baseline data regarding methemoglobinemia in Washington was collected, information on the condition disseminated to health care providers and geographic trends in disease occurrence were observed. Cases were ascertained from two separate data sources, a health care provider survey and the CHARS system. The data sources did not correlate well with each other indicating the need for additional work to establish the actual occurrence and distribution of methemoglobinemia. The etiology of the cases found in the CHARS data could not be determined causing further uncertainty in this study. If a case of methemoglobinemia is to be considered a "sentinel event" for illness associated with nitrates, additional work in this area is necessary to not only eliminate the occurrence of this health condition but to also identify other health outcomes which are associated with the ingestion of nitrates. This study is a beginning in the attempt to define the extent of the problem of nitrate in drinking water and its prevalence in Washington State. This work should be continued to fully understand the problem and design the appropriate interventions.