

Reye's Syndrome and Medication Use

Thomas J. Halpin, MD, MPH; Francis J. Holtzhauer, MS; Robert J. Campbell, MS; Lois J. Hall;
Adolfo Correa-Villaseñor, MD, MPH; Richard Lanese, PhD; Janet Rice, PhD; Eugene S. Hurwitz, MD

• **Ninety-seven Reye's syndrome (RS) cases in Ohio children with onsets from December 1978 through March 1980 were studied for medication use during their pre-RS illness. They were matched with 156 control subjects for age, race, sex, geographic location, time, and type of illness. Only the use of aspirin was reported by significantly more cases (97%, 94/97) than controls (71%, 110/156) during the pre-RS matched illness. Using a multiple logistic model to control for the presence of fever, headache, and sore throat statistically, the difference in aspirin use remained significant. Conversely, fewer cases (16%) took medications containing acetaminophen than controls (33%). In 87% of the cases receiving aspirin, their maximum daily dosage did not exceed recommended levels, but their doses were higher than those of controls receiving aspirin. No relationship was found between dosage and stage of RS encephalopathy.**

(JAMA 1982;248:687-691)

SINCE the initial description of Reye's syndrome (RS) as a distinct entity,¹ several studies have provided a more detailed characterization of the clinical, pathological, and epidemiologic aspects,²⁻⁵ but no clear understanding of the etiology of RS has

B and varicella zoster.^{6,7}

A number of medications have been investigated regarding their association with RS, with aspirin receiving particular attention. Previous epidemiologic studies report the proportion of patients using aspirin or aspirin-containing products before the onset of RS ranging from 53% to 100%.^{8,9,10} While these studies suggest an association, lack of control data makes interpretation difficult. However, recent case-control studies by Starko et al¹¹ and data from Michigan¹² suggest a possible association between aspirin and RS. The purpose of this study was to determine if the consumption of medications during the antecedent illness associated with RS differed from the medication consumption of control children who had uncomplicated viral illnesses.

SUBJECTS AND METHODS

A case-control study design was chosen

to assess medication consumption during the antecedent illness of RS. Ohio residents having onset of RS between Dec 1, 1978, and March 31, 1980, were classified as cases if they met the following criteria: an acute, noninflammatory encephalopathy as demonstrated by either a CSF level (if available) containing fewer than eight WBCs per cubic millimeter or cerebral edema without perivascular or meningeal inflammation associated with (1) microvesicular fatty metamorphosis of the liver diagnosed by biopsy or autopsy, or (2) a threefold or greater rise in SGOT, SGPT, or serum ammonia levels, and (3) no other, more reasonable explanation for the neurological or hepatic abnormalities.

To maintain uniform measurement of RS severity between participating medical centers, a modified Lovejoy staging system¹³ was used as specified by the Centers for Disease Control (CDC) RS reporting form.¹⁴ Stage 0 cases were awake and alert but had severe vomiting and elevated liver enzyme levels. Stage 1 cases were lethargic or difficult to arouse. Combativeness, delirium, or stupor was characteristic of stage 2 cases. Stages 3 through 5 were progressively deeper levels of coma.

A statewide surveillance system for identification of RS cases was established using the six major pediatric referral centers in Ohio. The physician and nurse coordinator who routinely cared for cases of RS were identified in each of these centers. In addition, infection control practitioners in all other Ohio hospitals having pediatric beds were contacted and requested to report cases of RS. Other sources of case reporting were the National Reye's Syndrome Foundation of Bryan, Ohio, local health departments, private physicians, and parents. The CDC, Ohio Department of Health (ODH), and each participating medical center obtained

**For editorial comment
see p 722.**

been achieved. Several investigators have reported an association of RS with various antecedent viral illnesses, particularly influenzae A and

From the Bureau of Preventive Medicine, Ohio Department of Health, Columbus (Dr Halpin, Messrs Holtzhauer and Campbell, and Ms Hall); the School of Preventive Medicine, Ohio State University, Columbus (Drs Lanese and Rice); and the Centers for Disease Control, Atlanta (Drs Correa-Villaseñor and Hurwitz). Dr Correa-Villaseñor is now with The Johns Hopkins School of Hygiene and Public Health, Baltimore.

Reprint requests to the Bureau of Preventive Medicine, Ohio Department of Health, 246 N High St, PO Box 118, Columbus, OH 43216 (Dr Halpin).

the approval of their respective committees on human experimentation before engaging in this study.

Patients admitted to one of the six pediatric referral centers were followed up by the nurse coordinator at that center. The nurses' duties included the rapid reporting of cases to the ODH and the subsequent interviewing of case and control families. Cases admitted to other hospitals were followed up by the closest nurse coordinator or by a member of the ODH study team.

Nurse coordinators and ODH staff members attended an orientation session in study protocol. In addition, two protocol review and update sessions were held during the 16 months of the study. No study data were reviewed at these meetings. Approximately every four months, infection control practitioners in all hospitals received notices stressing the continued importance of reporting RS cases.

When notified of a possible case, an ODH team member reviewed clinical and laboratory data to determine if the case definition had been met. Basic demographic information was also recorded. For each participating case in this study, two controls matched for age, race, sex, classroom, and type of antecedent illness were sought. Having only one control did not eliminate the case from the study. Informed consent was obtained from all subjects, their parents, or both.

The matching and selection of controls were completed by the ODH. If the case was of school age and school was in session, the principal was contacted and asked to provide a list of names of all children in the patient's class or homeroom who were of the same sex, race, and age (± 1 year) and were recently absent with an acute illness or appeared ill to the teacher or school nurse. On identifying potential controls, a random-number table was used to determine the order in which families were called. If the first call was unsuccessful (no answer, telephone in use, refused, or not matched), the next potential control family was called. If school was not in session or the child was not of school age, neighborhood playmates, church, day-care peers, or other patients of the RS child's pediatrician were sought as controls meeting the aforementioned matching criteria. If the case was of a minority race and no age- or sex-matched controls of that race could be identified, controls were selected from the age- and sex-matched children of the preponderant racial group of the area. Controls were matched for type of illness as described by the parent (eg, acute respiratory tract infection, varicella, mumps). A control was sought who had onset of illness from three days before to 14 days after onset of the antecedent illness of the case.

The Rey's Syndrome Study Questionnaire was personally administered to the parents of the cases and controls. A major portion of the questionnaire solicited information regarding symptoms and medications taken throughout the illness. Medication trade names, average dose per day, and number of days of administration were recorded. During the second influenza season, beginning in December 1979, the questionnaire was revised to distinguish more clearly between medications taken before and after the onset of vomiting associated with RS. This change also enabled quantitation of the dose in milligrams given each day. Body weights were obtained from medical records for cases but not for controls. Each medication was coded by its pharmacologic components using the 1979 *Physician's Desk Reference*¹⁷ and the *Handbook of Nonprescription Drugs*.¹⁸

Statistical analyses were done by the Biometrics Laboratory, Department of Preventive Medicine, The Ohio State University, Columbus. A matched-pair, multiple logistic analysis as described by Breslow et al¹⁹ was performed. Separate analyses were done for the first 12-month period (December 1978 through November 1979), for the remaining four months (December 1979 through March 1980), and for the combined 16-month study period.

RESULTS

Two hundred twenty-seven cases of RS were reported to the ODH from Dec 1, 1978, through March 31, 1980. Sixty-seven cases (30%) were classified as stage 0, and 160 (70%) were classified as stage 1 or greater. Only cases that progressed to stage 1 or greater were included in this analysis. Of the 160 cases stage 1 or greater, 25 (16%) refused to participate and 38 (24%) could not be matched with a control. Thus, 97 cases were included in the analysis.

These 97 cases were 57% female and 97% white, with 12% aged 1 through 4 years, 42% aged 5 through 9 years, 38% aged 10 through 14 years, and 7% aged 15 through 20 years. The antecedent illness for 85% of the cases was an acute upper respiratory tract infection (URTI); 10% had chickenpox, and 5% had other illnesses. Nineteen percent of the cases were confirmed by biopsy. Fifty-six percent of the cases were classified as stage 1, 21% were stage 2, 19% were stage 3 or greater, and 5% were fatal. Twenty percent of the cases occurred during the first winter respiratory illness season (December

1978 through March 1979), 13% from April through November 1979, and 67% in the second winter season (December 1979 through March 1980) associated with an influenza B epidemic.

The 97 cases included in this analysis were compared with the 63 nonparticipants and nonmatched cases. There were no statistically significant differences between these groups ($P \leq .05$, 2×2 contingency tables using the χ^2 statistic) for age, race, sex, severest stage, season of onset, or aspirin use (aspirin data not available for nonparticipant cases). Significantly fewer study cases (10%, 10/97) had chickenpox than nonparticipant and nonmatched cases (25%, 16/63).

The six referral centers reported 85% of the cases. Eighty-eight percent of the cases were matched with classroom controls. Approximately two potential controls were called to obtain a matched control willing to participate. Fifty-nine cases (61%) had two controls, while 38 cases (39%) had only one control. All case-control pairs in this study were matched for sex and race, except one black child who was matched with a white control. Eighty-nine percent of the 156 controls were matched within one year of age, 10% were matched within two years, and 1% within three years of age. Eighty percent of the control subjects had onset of illness from three days before to 14 days after the onset of their matched case's antecedent illness. The remaining control subjects had illness onsets from 15 days before to 21 days after the onset of their matched case's onset. The mean number of days from the first symptoms of the antecedent or matched illness to questionnaire completion was 11 days for cases and 16 days for controls.

A variety of medications was used by both cases and controls. These medications were grouped into 97 different generic categories. In reviewing these medication categories, only ten were used by 20% or more of either the cases or controls (Table 1). Although it is unlikely that a rarely used compound could be a significant risk factor, all compounds were statistically tested for differences between cases and controls (2×2 contingency tables and McNemar's test). Since many medications were being

tested, the significance level was set at $P < .01$. Only the use of aspirin, phenothiazines, and trimethobenzamide hydrochloride was significantly greater in cases than in controls. The revised questionnaire used in the second influenza season permitted analysis of medications given each day of the illness. All of the cases (63 of 63) in this study period received aspirin before the day of onset of severe vomiting (onset of RS). Only 42% of cases (5/12) receiving phenothiazines and 20% (1/5) receiving trimethobenzamide did so before the day of onset of RS. When the prevalence of these medications taken before onset of RS is analyzed, the difference from controls in use of these antiemetic medications is no longer statistically significant. Thus, only medications containing aspirin were used significantly more frequently by cases (97%) than by controls (71%) during the pre-RS matched illness.

Using a multiple logistic model to control for the presence of fever, headache, and sore throat (possible confounding variables for aspirin use), the estimate of the relative risk for development of RS with aspirin use was 11.5 for the entire study period ($P < .001$, Table 2). Similar results were obtained for each of the two separate study periods. Although the prevalence of fever was significantly greater in cases than in controls ($P < .01$), at each level of fever, the proportion of cases using aspirin was consistently higher (Table 3).

Conversely, significantly fewer cases (16%) took medications containing acetaminophen than controls (33%, $P < .01$). One percent of the cases took only acetaminophen and no aspirin, as compared with 19% of the controls. Fifteen percent of the cases and 14% of the controls received both aspirin and acetaminophen. Two percent of the cases and 11% of the controls took neither of these two compounds. Although some children received several compounds containing aspirin, 96% of the cases and 93% of the controls using aspirin received some or all of it in the form of the aspirin tablet. Ninety percent of the cases and 91% of controls reporting the use of aspirin identified specific brands. All subjects reporting the use of acetaminophen named specific

Medication	Cases, % (n=97)	Controls, % (n=156)
Aspirin	97	71
Alcohol	42	43
Vitamins	35	35
Acetaminophen	16	33
Phenothiazines	21†	4
Phenylpropanolamine hydrochloride	25	28
Guaifenesin	28	27
Dextromethorphan hydrobromide	16	22
Miscellaneous adsorbents	20	19
Chlorpheniramine maleate	18	20

*For cases, includes period from onset of antecedent illness until hospitalization for Reye's syndrome (RS).

†During the second study period, 12 (19%) of 64 cases received phenothiazines, but only 8% did so before the onset of RS (severe vomiting).

Variable	df	Unadjusted (Univariate)		Adjusted (Multivariate)	
		χ^2	P	χ^2	P
Headache	1	0.08	NS†	0.52	NS
Sore throat	1	1.62	NS	1.48	NS
Fever	1	8.60	<.01	5.44	<.05
Aspirin	1	30.18	<.001	27.00	<.001
Full model	4	37.20	<.001

Aspirin	Lower Bound‡	Estimate of Relative Risk	Upper Bound‡
Unadjusted (univariate)	2.87	11.69	47.61
Adjusted (multivariate)	2.73	11.50	48.42

*Ninety-seven cases and 156 controls. Computed by the Ohio State University Biometrics Laboratory.

†Not statistically significant at $P < .05$.

‡Ninety-five percent confidence interval.

Highest Temperature, °C (°F)	Cases n (%)	Controls n (%)
None	21/23 (91)	39/61 (64)
Unknown temperature	10/11 (91)	13/19 (68)
37.1-37.7 (98.7-99.9)	4/4 (100)	4/6 (67)
37.8-38.8 (100.0-101.9)	18/18 (100)	21/26 (81)
>38.9 (102.0)	41/41 (100)	33/44 (75)
Total	94/97 (97)	110/156 (71)

brands.

Cases and controls were analyzed regarding frequency of aspirin ingestion by type of antecedent illness. With varicella antecedents, all ten (100%) of the cases and seven (54%) of 13 of the controls took medications containing aspirin. With URTI and other prodromes, compounds containing aspirin were also taken more frequently in cases (97%, 84/87) than in controls (72%, 103/143). For five of the six referral centers, and each of

the four age intervals, a higher percentage of cases received aspirin than their matched controls. In the sixth center, the percentage was lower, but there were only six cases.

Decreased liquid intake also appeared to be associated with RS. Fifty-three percent of cases were reported to have decreased liquid intake during the antecedent illness, compared with 17% of controls. When this variable was added to the logistic model given in Table 2, both aspirin

and liquid intake were independently significant at $P < .001$.

Aspirin dosage per day was obtained and analyzed for 55 case and 60 control subjects receiving aspirin during the second study period. As body weight was not known for any control subjects, cases and controls were stratified by four age intervals (1 to 4 years; 5 to 9 years; 10 to 14 years; and 15 to 20 years) for dosage comparison. The logarithms of both the maximum milligrams per day and the mean milligrams per day for the days aspirin was given were determined. Cases and controls were compared using a three-way analysis of variance model including age interval and the presence of fever. Both the logarithms of the maximum and mean daily doses were significantly greater in cases than in controls ($P < .01$; no two- or three-way interactions significant at $P < .05$). Among controls for all intervals, both maximum and mean dosages were consistently higher in the presence of fever. This trend was totally absent in cases. Although dosages were significantly higher in cases, only 13% of the cases' maximum doses on any day exceeded the recommended dosage.

Body weight and aspirin dosage were obtained for 46 cases in the second study period. The maximum daily dose of aspirin ranged from 0 to 120 mg/kg, with a mean dose of 47 mg/kg (SD=22 mg/kg). Only 7% received a maximum daily dose exceeding 80 mg/kg. There was no significant difference in maximum daily dose using one-way analysis of variance among the different stages of RS.

COMMENT

This investigation focused on efforts to determine differences in medication use between RS cases and their matched controls. It is striking that while a large number of different medications were used both singly and in combination products by both case and control groups, cases received only one medication, aspirin, significantly more frequently during their antecedent illness than controls. An alternative analgesic, acetaminophen, showed a reverse relationship, with greater use in the control group. Furthermore, aspirin was the only medication used by almost all cases. No other factor than the antecedent

illness was more consistently associated with RS.

Reye's syndrome occurs in an estimated one to two children per 100,000 younger than 18 years.^{3,4} A relatively large number of cases associated with an influenza B epidemic occurred during this study, resulting in an annual rate exceeding four cases at stage 1 or greater per 100,000 children younger than 21 years. Even in epidemic periods, RS is a rare illness. Therefore, a retrospective (case-control) study design was used for this investigation to examine the possible association of medications and RS. However, this study design has some inherent limitations and biases that must be considered when interpreting any observed differences.

These may include selection, recall, and misclassification bias. Selection bias was reduced by choosing controls matched on several demographic variables, which may be associated with different patterns of medication use, and statistically controlling for potentially confounding differences in the antecedent illness.

The majority of controls in this study were chosen from the classroom cohort of the case and matched for age, race and sex, type of antecedent illness, and time of illness onset. Most RS cases occur in school-aged children during the winter months, making the classroom a good source for matched controls. As the antecedent illness in RS is uncomplicated, clinic- or hospital-based controls would be likely to have a different or more severe illness. Siblings were not used as controls, as they may be over-matched for some exposure variables. The type of antecedent illness is likely to be an important factor influencing medication use. In this study, illness matching was done on type of antecedent illness, not on specific symptoms and their severity. Data from this study indicate the antecedent illness in RS may be more severe than that observed in control subjects. Presence and degree of fever, as well as decreased liquid intake, were reported more by cases than controls. Since a hallmark of RS is severe vomiting, and the question related to decreased fluid intake during the matched illnesses did not specify when or how much of a decrease occurred, this possible risk factor

may be artifactual but certainly merits further study. Although cases may have been more severely ill, aspirin use was statistically significantly associated with cases after controlling for potentially confounding factors such as presence of fever, liquid intake, headache, and sore throat in multiple logistic models for the two separate and the combined study periods. Furthermore, for every level of fever, a greater proportion of cases than controls received aspirin. The reverse relationship of acetaminophen in controls and the absence of increased use for any other medication in the cases further reduce the likelihood that illness matching significantly biased the association of RS and aspirin.

Recall bias is also a potential problem in case-control studies. The time from onset of antecedent illness to the time of interview was longer in the controls than in cases, and RS is certainly a more significant event than an uncomplicated viral illness. It would have been difficult to shorten the time to the control interview and still match illness-onset dates. By the time an RS case is reported, a week or more may have elapsed since the beginning of the preceding viral illness. Contacting school authorities, obtaining classroom rosters, and calling and arranging a mutually convenient personal interview with the control family parents delayed completion of the control questionnaires. However, there are several observations that suggest that recall bias was not the explanation for the statistical difference in aspirin use between cases and controls. The prevalence of nonanalgesic medications reported for cases and controls is not significantly different, and, furthermore, acetaminophen use was reported by a greater proportion of controls. This would not be expected if there were a general tendency for case parents to recall all drugs with greater frequency. Finally, the vast majority of cases and controls could specify the trade name of the aspirin, so it does not seem likely that acetaminophen was in fact given and aspirin reported. These observations suggest that recall bias is not a major problem in this study.

It is also unlikely that the misclassification of case status would explain