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ORIGINAL REPORT

Utilization and Safety of Oral Acyclovir over an 8-Year Period

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SUMMARY

The primary purpose of this project was to develop and implement surveillance systems to monitor the short- and long-term safety of acyclovir in oral dosage forms in a general population, the Kaiser Permanente Northwest (KPNW) region membership. KPNW is a group model HMO providing comprehensive care to over 390,000 members located primarily in the Portland, Oregon-Vancouver, Washington metropolitan area. Data were collected from the automated outpatient prescription, hospital discharge, tumor registry, KPNW membership information, and from medical record reviews, over an 8-year period. The findings showed oral acyclovir use increased substantially, and females were twice as likely to receive oral acyclovir as males. Most use was short-term. When the hospitalizations of oral acyclovir users with select serious morbidities conditions were examined following the receipt of acyclovir, no temporal association was observed between exposure to oral acyclovir and the hospitalizations. Similarly, where oral acyclovir was being used within a time frame possibly associated with serious life-threatening conditions, other morbidities rather than acyclovir were the likely cause of the condition, and no mention was made in the medical record that acyclovir might have been involved in the condition. In summary, oral acyclovir was a safe drug within the use patterns of the HMO population over an 8-year period. © 1997 by John Wiley & Sons, Ltd.

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KEY WORDS — acyclovir; utilization; adverse effects

INTRODUCTION AND BACKGROUND

The purpose of this report is to assess the long-term utilization and safety of oral acyclovir in a large managed care setting. This is the final report of a research project to monitor the short- and long-range safety of oral acyclovir in the Kaiser Permanente Northwest (KPNW) region membership beginning in 1986. The project developed and implemented surveillance systems to capture hospitalizations occurring subsequent to exposure to oral acyclovir. At that time, oral acyclovir had exhibited an excellent safety profile in clinical trials of persons with primary and recurrent *Herpes simplex* virus (HSV) infections, but the safety of the drug in large general populations had not been established.

Beginning in 1986, the project collected acyclovir dispensing data and annual hospital discharges and cancer diagnoses occurring after acyclovir exposure. If a hospital discharge diagnosis appeared frequently or was biologically plausible, or if the exposure to oral acyclovir was substantial, the medical records of these patients were reviewed to determine if acyclovir could have been implicated in the diagnosis. This was done by searching the medical record for any notation that the diagnosis may have been associated with the drug.

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The first report examined the patterns of oral acyclovir use in the KPNW membership and applied the surveillance systems to the users over a 2-year period 1986–1987.[1] It appeared that most of the dispensings were for the treatment of genital herpes. Two-thirds of the dispensings were to females, and 80% of the dispensings were to KPNW members 15–45 years of age. Medical records were reviewed to monitor the short- and long-range safety of oral acyclovir in the Kaiser Permanente Northwest (KPNW) region membership. The medical record reviews of hospitalizations subsequent to oral acyclovir exposure found no information in the medical record implicating oral acyclovir in any of the diagnoses.

A second research initiative matched 1165 oral acyclovir users over a 2-year period with nonusers four-to-one.[2] The comparison of users and nonusers hospitalized for a select group of diseases found oral acyclovir users were no more likely than nonusers to be hospitalized for any of the selected group of diseases, with the exception of carpal tunnel syndrome. Subsequent review of the medical records of users with a diagnosis of carpal tunnel syndrome provided no indication that the drug was in any way implicated in the diagnosis.

A third research initiative, unpublished, compared hospital discharge diagnoses of renal calculi among oral acyclovir users with those for the KPNW membership from 1986–1991. The results indicated that the risk of being hospitalized for renal calculi was no greater among oral acyclovir users than among the KPNW membership in general.[3]

By 1994, a report reappraising the antiviral activity and therapeutic efficacy of acyclovir in intravenous and oral dose forms, found it to be an effective agent in the therapy and prophylaxis of *Herpes simplex* virus (HSV) and *Varicella zoster* virus (VZV) infections in immunocompetent and immunocompromised patients.[4] Summaries of acyclovir's safety over the first 10 years of marketing the drug showed the absence of major medical problems emerging from spontaneous reporting systems and from structured epidemiologic studies, and drug resistance to be rare.[5,6] Oral acyclovir has also been shown to be safe and efficacious in the suppression of genital herpes for up to 5 years.[7,8] Finally, data available have shown no increased risk of birth defects among women exposed to acyclovir during pregnancy.[9–11] However, no formal testing of the safety of the drug in human pregnancies has been done.[11] This study attempts to contribute additional knowledge about the long-term safety of the use of oral acyclovir in a large population over an 8-year period.

OBJECTIVES

Three objectives were identified: (1) to describe the patterns of acyclovir use in a general population over an 8-year period, 1986–1993; (2) to determine if oral acyclovir users in this population were at excess risk of hospitalizations for a selected list of serious discharge diagnoses relative to nonusers; and (3) to ascertain if any hospital discharges of life-threatening morbidities might have been associated with exposure to oral acyclovir among the population over the 8-year period.

METHODS

Study populations

The first study population was all KPNW members receiving a dispensing for acyclovir from 1 January 1986, through 31 December 1993 from the KPNW outpatient pharmacy database (see Appendix A for the list of acyclovir products).

The second study population was oral acyclovir users identified who had received one or more dispensings for either the 200-mg capsules or 800-mg tablets of acyclovir anytime during 1986 through 1993. A third study population was KPNW members with no dispensings of any dosage form of acyclovir during the 8-year period. The second and third study populations were subjected to the same exclusionary criteria. A fourth study population of the same oral acyclovir users was subjected to slightly different exclusionary criteria than the second and third study populations.

Sources of data and data collection

The sources of data were KPNW's automated outpatient prescription system, the automated hospital discharge system, the outside claims and referral file, and the membership information file. The following data were collected from these sources: all dispensings of acyclovir, hospitalizations for select discharge diagnoses occurring after specified periods of exposure to oral acyclovir, and KPNW eligibility of users and nonusers of acyclovir, during the 8-year period.

Serious morbidities of interest. A list of select discharge diagnoses was identified. The list contained biologically plausible morbidities from exposure to acyclovir and diagnoses involving organs known to be susceptible to damage from exposure to drugs (Appendix B).

Life-threatening morbidities of interest. A list of life-threatening morbidities was also identified with the aid of clinician expertise (Appendix C).

Measures

Episodes of KPNW eligibility. Episodes of KPNW eligibility were established for oral acyclovir users and nonusers. Episodes of KPNW eligibility over the 8 years were defined as periods of KPNW membership with gaps in eligibility of no greater than 60 days. Most gaps of 60 days or less are largely administrative and not true loss of KPNW eligibility. Users and nonusers with at least one episode of eligibility between 1986 and 1993 numbered 654,184. See Appendix D for the annual person-years at risk of KPNW membership by gender and age.

From the total of 12,502 oral acyclovir users during the 8-year period, users with no episodes of KPNW eligibility ($N = 540$), with less than 2 years of KPNW eligibility prior to their first dispensing of oral acyclovir ($N = 3980$), and users with no eligibility after their first dispensing of oral acyclovir ($N = 260$) were excluded. This left a population of 7722 users.

Episodes of oral acyclovir use. Dispensings to users were employed to construct episodes of oral acyclovir use. Two consecutive dispensings were linked if the difference between the dispense dates was less than or equal to the days' supply plus 10% of the dispensed quantity. If dispensings did not link, a new episode of use began with the next dispensing, if any.

Periods at risk of serious morbidity. Thirty-day and 90-day periods at risk of serious morbidity were constructed. Thirty-day periods linked episodes of oral acyclovir use with gaps of 30 days or less between them. Ninety-day periods linked episodes of oral acyclovir use with gaps of 90 days or less between them.

Matching users to nonusers. Oral acyclovir users were matched to nonusers by age (year of birth), gender, and KPNW eligibility between 1984 and 1993. The eligibility matching period began in 1984 to assure similar eligibility during the 2 years prior to the first dispensing.

To simplify the matching process, the eligibility period 1984–1993 was broken down into 6-month segments. A user and nonuser were considered a match if they had the same eligibility status during each of the 6-month periods, even if their eligibility start and end dates were not an exact match.

Each user was matched to up to five nonusers because exclusionary criteria had not been applied to the study population. By selecting multiple nonuser matches, a user was not dropped from the analysis until all five of the matched nonusers had been excluded by applying the criteria described below.

Exclusions (other than eligibility). Additional exclusions were made after the matching process. This was done because the exclusionary conditions were those present in the 2 years prior to the users' first dispensing of oral acyclovir. Users were excluded if they had been hospitalized for one of the diagnoses of interest (Appendix B) during the 2 years prior to their first dispensing of oral acyclovir. To determine the nonuser exclusions, it was first necessary to know with which user they were matched and the date of that user's first dispensing of oral acyclovir. Nonusers with the selected discharge diagnoses were also excluded, using the first dispensing date from their matched user as the reference date for the prior 2 years. This criterion excluded a total of 124 users and 375 nonusers.

Second, if the user or nonuser had received an organ transplant at any time, they were excluded. Transplant recipients were identified via claims for reimbursement for outside care (most transplants are performed at non-KPNW hospitals) or via multiple prescriptions for immunosuppressant drugs (see Appendix E). A total of 55 users and 53 nonusers were excluded.

Third, if the user or nonuser had an indication of AIDS at any time, they were excluded. AIDS patients were identified via hospital admissions with certain diagnoses or via dispensing of selected drugs (see Appendix F). This criterion excluded a total of 124 users and 19 nonusers.

Fourth, if the user or nonuser had a diagnosis of a malignancy in the 2 years prior to the user's first dispense date, they were excluded. The KPNW Tumor Registry was used to identify users with a

diagnosis of malignant neoplasms with the exception of non-melanoma skin cancers. A total of 212 users and 425 nonusers were excluded for malignancies.

Fifth, if the user and the nonuser had a different drug benefit status (i.e. one had a prepaid drug benefit and one did not), the pairing was dropped. Drug benefit status was checked at two points in time: the year-end prior to the user's first dispense date and the year-end before the user or nonuser's termination date (or year-end 1993, if the user did not terminate membership). A total of 736 users and 9814 nonusers were excluded on this basis.

Finally, 15 users were dropped because all of their matched nonusers had been excluded. The resulting file contained 6456 users and 15,391 nonusers. For users with multiple matched nonusers, one matched nonuser was selected at random.

The study population of 6456 users was compared with the users that had been excluded. The two groups were similar in terms of age (a median age of 46 for both groups), gender (67 versus 68% female), and total exposure to acyclovir (a median of 45 days for both groups). It did not appear that the exclusions produced a nonrepresentative sample of oral acyclovir users for analysis.

Oral acyclovir users total days of acyclovir-exposed and unexposed risk of select serious morbidities. The number of days for a period of exposed risk per user — where outcome was the risk of being hospitalized for one of the select serious morbidities of interest while exposed to acyclovir — was the sum of the total days of oral acyclovir use plus up to 30 days subsequent to the end of exposure for one analysis and up to 90 days for a second analysis. If the number of days between episodes of risk was greater than 30 days for one analysis, and greater than 90 days for the other analysis, new periods at risk began and two total days of exposed risk per user were calculated. Each was the sum of the number of days in that period of exposed risk using the 30-day criterion and the sum of the number of days of exposed risk in that period using the 90-day criterion.

Also summed, was the total number of days that users were at risk of a hospitalization for a select serious morbidity of interest while not exposed to acyclovir, or total days of unexposed risk per user.

Oral acyclovir users with life-threatening conditions. The fourth study population was oral acyclovir users with life-threatening conditions. The selection of and exclusions of oral acyclovir users with life-threatening conditions were the same as for the select serious morbidities except: (1) no matched nonusers were selected, so drug benefit data were not checked; (2) the AIDS exclusions included only ICD-9 codes 42. XX; and (3) the users had to have only 3 months of prior KPNW eligibility. The number of oral acyclovir users at risk of a life-threatening condition over the 8-year period was 10,457.

Hospital discharges for any of the life-threatening morbidities that occurred within a defined period of time subsequent to a dispensing of oral acyclovir were identified. The amount of time it would take for these specific morbidities to manifest themselves subsequent to taking a drug were estimated by a research clinician with the aid of a toxicologist.

Analysis Design

Patterns of utilization were examined using frequency distributions and measures of central tendency.

The analyses comparing the oral acylovir users and nonusers on hospital events for groupings of the less serious morbidities of interest employed a time-to-first-event approach. The denominator for those having an event was based on the person-years from the date of first dispensing to the date of the first event for users, and person-years at risk from the reference date to the first event for nonusers. For users and nonusers without an event, the denominator was their total person-years at risk. We used only the first event, since subsequent events with the same discharge diagnoses could be influenced by the first event. Relative risk was measured by ratio of the incidence event rate among users to the incidence event ratio among nonusers. Incidence rate ratios and their exact confidence intervals were estimated for each morbidity grouping of interest.[12]

A second analysis used the same statistical technique to compare the hospitalization rates for each of the morbidity groupings of interest during exposed and unexposed risk periods of users, using both the 30- and 90-day periods at risk criteria. This analysis included all events.

Oral acyclovir users with life-threatening conditions within the specified time ranges were examined by medical records review to assess any possible association with the use of acyclovir.

Table 1 — Users of 200-mg acyclovir capsules/1000 annual person-years at risk by sex and age

	1986	1987	1988	1989	1990	1991	1992	1993
Females								
0–19	0.7	1.1	1.7	1.3	1.9	2.2	2.7	3.6
20–34	6.1	8.1	9.5	12.1	14.6	16.3	19.9	20.9
35–49	3.5	5.2	7.6	9.2	11.8	14.8	17.7	19.9
50–64	1.5	2.2	3.6	5.1	6.2	8.4	8.5	9.9
65–84	1.5	2.8	3.5	4.3	6.7	8.3	5.7	6.4
85+	0.6	2.5	4.2	2.2	4.1	8.9	2.2	3.6
All Ages	2.7	3.9	5.2	6.3	8.1	9.8	11.0	12.3
Males								
0–19	0.2	0.4	0.4	0.6	0.6	0.7	1.1	1.2
20–34	2.4	3.4	3.7	4.5	6.2	6.7	7.4	7.4
35–49	2.6	3.4	4.0	5.5	5.4	7.4	8.3	8.5
50–64	0.9	1.7	2.3	2.7	3.8	5.2	4.1	5.8
65–84	0.7	1.4	2.3	2.9	4.5	6.1	3.3	3.4
85+	0.6	1.0	0.9	1.3	2.9	3.1	1.5	1.4
All Ages	1.5	2.2	2.7	3.4	4.2	5.3	5.4	5.8
Total	2.1	3.1	4.0	4.9	6.2	7.7	8.3	9.2

RESULTS

From 1986 through 1993, 51,073 prescriptions for acyclovir were dispensed to KPNW members from KPNW outpatient pharmacies. Of these, 67.1% were for the 200-mg capsules and 4.0% were for the 800-mg tablets. Almost all of the remaining dispensings were for the ointment.

These dispensings were received by 17,834 KPNW members. Users of the 200-mg capsules comprised 61.0% of all acyclovir users, and users of the 800-mg tablets comprised an additional 10.0% of all users. Among users, 68.7% were females.

Acyclovir 200-mg capsule users

Table 1 shows the use rate of acyclovir 200-mg capsules among the KPNW membership each year over the 8-year period, 1986–1993. The rate increased almost five-fold. Females were more than twice as likely to be exposed as were males. Females between the ages of 20 and 49 were the sex–age group most likely to be exposed to the 200-mg capsules.

Annual days of exposure to acyclovir 200-mg capsules. Over the 8-year period, the mean days of annual exposure increased from about 31 to 38 days among females and from about 42 to 44 days among males. Males consistently had more days of exposure than females. Males and females 35–49 years of age had the longest mean number of days of exposure to the 200-mg capsules each year, ranging from 37 days in 1987 to 45 days in 1993 among females, and from 44 days in 1987 to 54 days in 1993 among males.

Percentage of time-at-risk of exposure that KPNW users of 200-mg capsules were exposed to the drug. Overall, the percentage of time-at-risk of exposure that the users were exposed to the drug was around 10% and increased slightly over time and did not differ much by gender. Among both sexes, the percentage of time users were exposed to the drug peaked in the age group 35–49, at 14% among females in 1993, and at 16% among males in 1993.

Total number of days KPNW members were exposed to acyclovir 200-mg capsules. Over the 8-year period, the mean days exposed to the drug per user was about 60 days. Males had more total days exposed than females, 69 versus 54. Males and females 35–49 years of age had the most total days of exposure of any sex and age group, 103 and 74 days respectively.

Other data indicated that 22 users (0.2%) took the drug for 5 years or longer, and 10 of these users had one continuous episode of use of 5 years or longer during the 8-year period. An additional 64 users (0.6%) used the drug from 3 to 5 years,

and 34 of these had one continuous episode of use from 3 to 5 years.

Acyclovir 800-mg tablet users

Table 2 shows the proportions of the KPNW membership exposed to acyclovir 800-mg tablets. The dose form became available in 1991 and is intended primarily for the treatment of *Herpes zoster*. Between 1992 and 1993, the proportion of female users increased while the proportion of male users did not. As expected, the proportions exposed increased with age; the age group 65 and over of both sexes had the greatest exposure to this dosage strength.

The annual number of days of exposure to acyclovir 800-mg tablets appeared to increase slightly from 1992 to 1993 and was around 14 days for most users. By 1993, mean annual days of exposure were highest among male and female users 35–49 years of age, 22 and 18 days respectively.

Overall, the percentage of time-at-risk that the 800-mg tablet users were exposed to this dose form increased slightly over time, from under 4% to 4.5% in 1993. Male users were exposed for a somewhat larger proportion of their time-at-risk than female users. Among female users, the proportion of time-at-risk using the tablets was highest for those in the age group 35–49 and for males it was those in the age group 20–34.

The mean total days exposed to the 800-mg dose form over the 3-year period was about 14 days. Males had slightly more mean total days of exposure than females, 16 versus 15. Males and females 35–49 years of age had the most total days of exposure of any sex and age group, 18 and 20 days respectively.

Acyclovir ointment users

Exposure to acyclovir ointment peaked at 4.2 users/1000 KPNW members in 1991 then decreased to 1.3 in 1993 with its removal from the KPNW drug formulary. Females were consistently more than twice as likely than males to use the ointment. At the peak year of use, the largest proportion of users was females between the ages of 20 and 49 (6.2 users/1000).

Comparing users and nonusers on hospitalizations

Table 3 shows that, using the 30-day period at-risk criterion, the relative risks of a hospitalization for a serious morbidity of interest were not significantly higher among oral acyclovir users. When the 90-day period at-risk criterion was applied (Table 4), a significantly greater risk of hospitalization for a skin-related condition was observed among the users.

Table 2 — Users of 800-mg acyclovir tablets/1000 annual person-years at risk by sex and age

	1991	1992	1993
Females			
0–19	0.0	0.2	0.2
20–34	0.3	1.5	1.8
35–49	0.3	1.7	2.2
50–64	0.8	3.1	4.4
65–84	1.9	7.2	8.3
85+	1.6	4.5	8.3
All ages	0.5	2.2	2.7
Males			
0–19	0.0	0.1	0.2
20–34	0.1	1.2	1.7
35–49	0.3	1.7	1.8
50–64	0.7	3.0	2.6
65–84	1.1	6.5	6.3
85+	1.7	5.7	7.1
All ages	0.3	1.8	1.9
Total	0.4	2.0	2.3

Comparing users during acyclovir exposed and nonexposed periods at risk

Tables 5 and 6 show no significant excess risk of hospitalization among oral acyclovir users during their exposed periods for any of the serious morbidities of interest using either the 30-day or 90-day period at-risk criteria

Since skin-related conditions were the only morbidity that showed an excess risk among oral acyclovir users, additional data about the hospital discharges of these six oral acyclovir users who had been hospitalized for a skin-related condition were obtained to see if acyclovir could have been implicated in the morbidity.

Among the six, three were male and three were female. Their ages ranged from 30 to 84. Three of the discharges, two for dermatitis and one for unspecified pruritic disorder were attributed to the adverse effects of drugs other than acyclovir. Two discharges were for rash. One had received only five 200-mg acyclovir capsules prior to her hospitalization, while the other, who had concurrent diagnoses of malignant neoplasms of the liver

Table 3 — Comparison of users and matched non-users — 30-day period-at-risk (PAR)

Diagnosis group	Users ($n = 6456$) Cases	Time in person-years	Matched nonusers Cases	Time in person-years	Rel. risk	Exact 95% CI
Dementia	1	1959	5	14,221	1.45	0.0–12.9
Delirium	1	1960	3	14,229	2.42	0.1–31.0
Depressive psychosis	2	1959	21	14,176	0.69	0.1–2.8
Anxiety state	1	1959	9	14,207	0.81	0.0–5.9
Other mental disorders	1	1959	2	14,227	3.63	0.1–73.4
Liver/pancreas disease	0	1960	4	14,221	0.00	—
GI hemorrhage	4	1959	17	14,174	1.70	0.4–5.2
Renal disease	1	1959	6	14,218	1.21	0.0–10.0
Renal failure	0	1960	9	14,211	0.00	—
Calculus of kidney	1	1959	1	14,230	7.26	0.1–719.1
Skin-related	3	1959	5	14,212	4.35	0.7–23.0
Dizziness	1	1960	4	14,217	1.81	0.1–18.7
Headache	1	1959	5	14,221	1.45	0.0–12.9
Miscellaneous	0	1960	7	14,217	0.00	—

+, Increased risk for acyclovir users.
–, Decreased risk for acyclovir users.

Table 4 — Comparison of users and matched non-users — 90-day period-at-risk (PAR)

Diagnosis group	Users ($n = 6456$) Cases	Time in person-years	Matched nonusers Cases	Time in person-years	Rel. risk	Exact 95% CI
Dementia	4	3721	5	14,221	3.06	0.6–14.4
Delirium	1	3721	3	14,229	1.27	0.0–16.3
Depressive psychosis	4	3721	21	14,176	0.73	0.2–2.1
Anxiety state	3	3721	9	14,207	1.27	0.2–5.1
Other mental disorders	1	3720	2	14,227	1.91	0.0–38.7
Liver/pancreas disease	0	3721	4	14,221	0.00	—
GI hemorrhage	5	3720	17	14,174	1.12	0.3–3.1
Renal disease	1	3721	6	14,218	0.64	0.0–5.3
Renal failure	0	3721	9	14,211	0.00	—
Calculus of kidney	1	3721	1	14,230	3.82	0.0–378.6
Skin-related	6	3720	5	14,212	4.58	1.1–18.7
Dizziness	1	3721	4	14,217	0.96	0.4–9.8
Headache	4	3719	5	14,221	3.06	0.6–14.4
Miscellaneous	2	3721	7	14,217	1.09	0.1–5.7

+, Increased risk for acyclovir users.
–, Decreased risk for acyclovir users.

and lung, had received a total of 100,000 mg of acyclovir prior to his hospitalization. The final user had a diagnosis of urticaria, unspecified and had received a total of 4000 mg (20 200-mg capsules) of acyclovir prior to her hospitalization.

Oral acyclovir users with life-threatening conditions

Seven oral acyclovir users had diagnoses of life-threatening morbidities during the at-risk period after an oral acyclovir dispensing. Five were female and two were male and their ages ranged from 19 to 64. Four had discharge diagnoses of aplastic anemia, two females had diagnoses of agranulocytosis, and one male had a diagnosis of toxic myopathy. None had had extensive exposure to oral acyclovir prior to their reference hospitalization.

Among the four users with a discharge diagnosis of aplastic anemia, one had chronic myelogenous leukemia, had a bone marrow transplant, and the

Table 5 — Comparison of users' exposed and unexposed periods — 30-day period-at-risk (PAR)

Diagnosis group	Discharges during exposed periods ($n = 6456$)	Discharges during unexposed periods ($n = 6456$)	Rel. risk	Exact 95% CI
Dementia	1	8	1.18	0.0–5.8
Delirium	1	5	1.77	0.0–11.2
Depressive psychosis	2	20	0.42	0.1–2.6
Anxiety state	1	20	0.49	0.0–2.0
Other mental disorders	1	7	0.41	0.0–7.1
Liver/pancreas disease	0	4	0.00	–
GI hemorrhage	4	35	1.25	0.2–2.0
Renal disease	1	41	0.24	0.0–0.9
Renal failure	0	11	0.00	–
Calculus of kidney	1	5	1.62	0.0–11.2
Skin-related	3	10	1.95	0.3–7.4
Dizziness	1	7	1.33	0.0–7.1
Headache	1	12	0.64	0.0–3.5
Miscellaneous	0	6	0.00	–

+, Increased risk for acyclovir users.
–, Decreased risk for acyclovir users.

Table 6 — Comparison of users' exposed and unexposed periods — 90-day period-at-risk (PAR)

Diagnosis group	Discharges during exposed periods ($n = 6456$)	Discharges during unexposed periods ($n = 6456$)	Rel. risk	Exact 95% CI
Dementia	4	5	3.71	0.5–0.8
Delirium	1	5	0.75	0.0–5.1
Depressive psychosis	4	18	0.72	0.2–2.0
Anxiety state	3	18	0.66	0.1–1.6
Other mental disorders	1	7	0.05	0.0–3.2
Liver/pancreas disease	0	4	0.00	–
GI hemorrhage	5	34	0.62	0.1–1.1
Renal disease	1	41	0.09	0.0–0.4
Renal failure	0	11	0.00	–
Calculus of kidney	1	5	0.67	0.0–5.1
Skin-related	6	7	3.50	0.7–8.6
Dizziness	1	7	0.25	0.0–3.2
Headache	4	9	1.48	0.3–4.5
Miscellaneous	2	4	0.64	0.1–10.2

+, Increased risk for acyclovir users.
–, Decreased risk for acyclovir users.

medical record mentioned the diagnosis of aplastic anemia to be secondary to the leukemia and chemotherapy treatment. A second user had acute lymphocytic leukemia with pancytopenia present during a prior hospitalization. The discharge diagnosis was consistent with the leukemia and multiple chemotherapies she was taking. The third user had Hodgkin's disease and had significant anemia and low platelets noted prior to her first acyclovir exposure. The medical record of the fourth user with a discharge diagnosis of aplastic anemia could not be located. She had received a dispensing of 50 800-mg tablets, a 25-day supply, prior to the discharge diagnosis.

SUMMARY AND DISCUSSION

Since the 800-mg tablets were only available for a little more than 2 years of the 8-year period, and

the ointment was removed from the KPNW drug formulary in 1992, the summary and discussion focus on the 200-mg capsule dosage form.

The number of oral acyclovir users increased by about five-fold over the 8-year period. Use was most frequent in the younger adult age groups and females were much more likely to be users than males.

The consistently small mean total number and variance in the total number of days of annual exposure to oral acyclovir suggest that most users in KPNW were using the drug for acute occurrences and recurrences of the condition, and few were using it in a maintenance regimen to prevent recurrences. The fact that users appeared to take the drug only a small proportion of their time-at-risk strengthened this interpretation. They did not take the drug about 90% of their time-at-risk of exposure to the drug.

Long-term use of the drug was infrequent. About two-thirds of male users 35–49, the age group with the largest mean total number of days exposed to acyclovir, took the drug for less than 1 year over the 8-year period. Two-thirds or less of females in the age groups 20 through 49, the age groups with the largest proportion of acyclovir users, took the drug for about 8 months or less over the 8-year period. The maximum total days of use was somewhat less than 7 years.

A number of factors could have been responsible for the almost five-fold increase in the use of 200-mg acyclovir over the time period. Both prescribers and patients should have become more aware of the effectiveness and the safety of the drug in systemic treatment of herpes viral infections, primarily genital herpes. In addition, the incidence of the disease could have increased. Also, incident cases became prevalent cases as it was shown that daily maintenance doses of acyclovir could delay or prevent recurrences of the condition.

Since genital herpes is a sexually transmitted disease, the largest proportion of users was expected to be found among younger adults, the most sexually active. The finding that females were twice as likely to be users as males was consistent with earlier data from this setting and was consistent with another report indicating that two-thirds of the users of acyclovir were female.[1,13]

Among the serious morbidities of interest, the use of oral acyclovir was associated with an increase only in the risk of a hospitalization for skin-related conditions. A review of the automated discharge summary indicated that in the infrequent situations where acyclovir could have been associated with the skin-related morbidities, the extent of exposure to oral acyclovir was minimal, and given the multiple discharge diagnoses of these users, other drug exposures were probably more likely to be the cause of the condition.

Regarding the possible association of acyclovir exposure with life-threatening conditions, it appeared that the multiple disease states present among users with such conditions were far more likely to be the reason for the condition rather than their limited exposures to oral acyclovir.

CONCLUSIONS

The use of acyclovir increased substantially over time in the KPNW membership, with females twice as likely to receive oral acyclovir as males. Most use was short term rather than long term. As a result, even though surveillance covered 8 years, few long-term users of oral acyclovir were identified, limiting the surveillance of long-term users for drug safety.

Detailed examination of the potential excess risk of hospitalization for certain serious conditions among users found the conditions not related to the use of oral acyclovir. Similarly, where oral acyclovir was being used within a time frame of serious life-threatening conditions, other disease states were far more likely to be the cause of the life-threatening condition. In addition, no mention was made in the medical record that any of the conditions were the possible adverse consequences of the antiviral use.

All efforts undertaken to investigate the safety of oral acyclovir over the 8-year period showed the drug to be very safe within the use patterns of the drug in the HMO population.

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REFERENCES

1. Johnson, R. E., Mullooly J. P., Valanis, B. G., Andrews, E. B. and Tilson, H. H. Acyclovir use and its surveillance in a general population. *Drug Intelligence and Clinical Pharmacy: Annals of Pharmacotherapy* 1990; **24**: 624–628.

2. Johnson, R. E., Mullooly, J. P., Valanis, B. G., *et al*. Method of examining oral acyclovir use for adverse events. *Journal of Clinical Research in Pharmacoepidemiology* 1991; **5**: 331–345.
3. Johnson, R. E. and Mullooly, J. P. Oral acyclovir use and renal calculi. Unpublished manuscript, Center for Health Research, Kaiser Permanente Northwest Region, Portland, OR 97227, October 1992.
4. Wagstaff, A. J., Faulds, D. and Goa, K. L. Aciclovir — a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47**: 153–205.
5. Tilson, H. H., Engle, C. R. and Andrews, E. B. Safety of acyclovir: a summary of the first 10 years experience. *Journal of Medical Virology* 1993; Suppl. 1: 67–73.
6. Goldberg, L. H., Kaufman, R., Kurtz, T. O., *et al*. Long-term suppression of recurrent genital herpes with acyclovir — a 5-year benchmark. *Archives of Dermatology* 1993; **129**: 582–587.
7. Whitley, R. J. and Gnann J. W. Acyclovir: a decade later. *New England Journal of Medicine* 1992; **327**: 782–788.
8. Baker, D. A. Long-term suppressive therapy with acyclovir for recurrent genital herpes. *Journal of International Medical Research* 1994; 22 (Suppl. 1): 24A–32A.
9. Andrews, E. B., Yankaskas, B. C., Cordero, J. F., *et al*. Acyclovir in pregnancy registry: six years' experience. *Obstetrics and Gynecology* 1992; **79**: 7–13.
10. Spangler, J. G., Kirk, J. K. and Knudson, M. P. Use and safety of acyclovir in pregnancy. *Journal of Family Practice* 1994; **38**: 186–191.
11. Pregnancy outcomes — following systemic prenatal acyclovir exposure — June 1, 1984–June 30, 1993. *Mortality and Morbidity Weekly Report* 1993; **42**: 806–809.
12. Rothman K. J. *Modern Epidemiology*. Little, Brown and Company, Boston/Toronto, p.167.
13. Bjornson D. C. and Wertheimer A. I. Patterns of use: topical and oral acyclovir. *Journal of Pharmacoepidemiology* 1990; **1:** 49–59.

APPENDIX A

ACYCLOVIR PRODUCTS

Oral
200-mg capsules
200-mg/5 ml suspension
800-mg tablet
Topical
5% ointment

APPENDIX B

SERIOUS MORBIDITIES OF INTEREST

Morbidity and ICD-9 code	
Dementia:	
290.1X	presenile dementia
290.4X	arteriosclerotic dementia
Delirium	
293.0	acute delirium
293.1	subacute delirium
Depressive psychosis	
298.X	depressive type psychosis
Anxiety state	
300.00	anxiety state, unspecified
300.01	panic disorder
Other mental disorders	
295.X	schizophrenic disorders
300.4	neurotic depression
300.9	unspecified neurotic disorder
Liver/pancreas	
573.8	liver disorders NEC
573.9	liver disorder NOS
577.1–9	diseases of the pancreas
GI hemorrhage	
578.X	GI hemorrhage
578.9	hemorrhage of GI tract, unspecified
Renal disease	
581.XX	nephrotic syndrome
582.XX	chronic glomerulonephritis
583.XX	nephritis and nephropathy
Renal failure	
585	chronic renal failure
586	renal failure NOS
Calculus of kidney	
592.0	calculus of kidney
Skin-Related	
693.0	dermatitis due to drugs and medicines
698.9	pruritis
708.0	allergic urticaria
708.9	urticaria, unspecified
782.1	rash and unspecified skin eruption
Dizziness	
780.4	dizziness and giddiness
Headache	
784.0	headache
Miscellaneous	
281.0	pernicious anemia
348.3	encephalopathy, unspecified
518.4	acute edema of the lung, unspecified
784.5	speech disorder

APPENDIX C
LIFE-THREATENING MORBIDITIES OF INTEREST (WITH TIME-AT-RISK PERIODS)

Morbidity and ICD-9 code		Estimated number of days
Anemia		
283.X	acquired hemolytic anemias	1
284.8	aplastic anemias NEC	90
284.9	aplastic anemia NOS	
Blood dyscrasias		
287.4	secondary thrombocytopenia	2–4
287.5	thrombocytopenia, unspecified	
Agranulocytosis		
288.0	agranulocytosis	10–20
Circulatory system		
425.4	primary cardiomyopathies	15–90
Nervous system		
292.XX	drug psychoses	1–7
349.82	toxic encephalopathy	1–15
359.4	toxic myopathy	
Liver		
570	acute necrosis of liver	3–5
572.2	hepatic coma	4–6
573.3	hepatitis NOS	3–5
573.4	hepatic infarction	<1
Pancreas		
577.0	acute pancreatitis	2–7
Kidney		
584.5	lower nephron nephrosis	<1
584.X	acute renal failure	3
Skin conditions		
695.1	erythema multiforme (Stevens-Johnson syndrome, toxic epidermal necrolysis)	2
695.89	exfoliate dermatitis	5
General symptoms		
780.1	hallucinations	
780.3	convulsions	
Shock without trauma		
785.5X	shock without mention of trauma	<1
Sudden death, cause unknown		
799.0	asphyxia	<1
799.1	respiratory failure	<1
Overdose		
961.7	poisoning by antiviral drugs	<1
Anaphylactic shock		
995.0	anaphylactic shock	<1

APPENDIX D
ANNUAL PERSON-YEARS AT RISK BY SEX AND AGE

	1986	1987	1988	1989	1990	1991	1992	1993
Females								
0–19	44,963	46,366	50,049	54,102	55,702	55,360	55,310	55,220
20–34	34,182	34,073	36,075	38,978	40,612	39,961	39,107	38,399
35–49	33,301	35,485	39,038	43,058	46,012	47,400	48,616	49,790
50–64	19,997	21,143	22,623	24,148	25,489	25,568	27,719	29,230
65–84	17,810	19,495	20,912	22,385	23,617	23,929	23,818	23,777
85+	1,752	1,969	2,135	2,294	2,447	2,572	2,693	2,805
All ages	132,005	158,530	170,831	184,964	193,878	194,788	197,261	199,219
Males								
0–19	47,040	48,587	52,382	56,482	58,104	57,695	57,545	57,379
20–34	26,967	26,874	28,983	31,989	33,691	32,850	31,682	31,117
35–49	30,472	32,286	35,487	39,101	41,747	42,672	43,129	43,555
50–64	17,926	18,933	20,334	21,964	23,445	24,351	25,293	26,646
65–84	13,669	14,997	16,121	17,285	18,313	18,717	18,842	18,997
85+	751	847	928	1,021	1,111	1,168	1,222	1,271
All ages	136,824	142,523	154,233	169,841	176,410	177,453	177,712	178,965
Total	288,828	301,053	325,064	352,805	370,288	372,241	374,973	378,184

APPENDIX E
ORGAN TRANSPLANT EXCLUSIONS

Outside care and referral type exclusions

TRB	bone marrow
TRC	cornea
TRG,THL	heart/lung
TRH	heart
TRK	kidney
TRL	liver
TRP	pancreas
TSL	single lung
TRP	kidney/pancreas

Drug product exclusions by name

- azathioprine
- cyclosporin
- prednisone

(Users and nonusers were excluded if they had one or more dispensings for azathioprine or cyclosporin, and a total of five or more dispensings for azathioprine, cyclosporin and/or prednisone)

APPENDIX F
AIDS EXCLUSIONS

Inpatient discharge diagnosis by ICD-9 codes

42.XX	HIV infection with specified conditions
43.XX	HIV infection causing other specified conditions
44.XX	other HIV infection

The inpatient admission and discharge file provides for up to nine discharge diagnoses. Any time the above diagnoses were listed, it became an exclusion

Drug products
- vidarabine
- zidovudine
- pentamidine isethionate
- gancyclovir sodium
- didanosine

Users and nonusers with one or more dispensings for any of these drugs were excluded

