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Preliminary communication

Rates of flu-like infection in patients with affective illness

Jay D. Amsterdam[a,*], Felipe García-España[a], Janusz Rybakowski[b]

[a]*Depression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104, USA*

[b]*Department of Adult Psychiatry, University of Medical Sciences, Poznan, Poland, and Medical Academy of Bydgoszcz, Bydgoszcz, Poland*

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Abstract

Studies of immunologic profiles of depressed patients are suggestive of chronic viral infection and several investigators have found specific viral protein in some depressed patients. Moreover, several psychotropic drugs have anti-viral activity and can inhibit viral replication. In this preliminary report, we retrospectively examined the rate of reported flu-like episodes before and during psychotropic drug treatment in 236 affectively ill patients: 177 receiving lithium prophylaxis and 59 receiving chronic antidepressant medication. We observed a small but significant reduction in the mean rate of reported flu-like illness during lithium therapy ($P < 0.001$), with a greater reduction in men vs. women ($P < 0.05$). We also found a modest reduction in reported flu-like illness during chronic treatment with antidepressants ($P = 0.08$). Although these observations are preliminary in nature, they complement earlier reports that some psychotropic drugs may have anti-viral activity. © 1998 Elsevier Science B.V.

Keywords: Viral infections; Anti-viral; Psychotropic drugs; Lithium; Affective disorders

1. Introduction

There is considerable evidence suggesting an association between some psychiatric disorders and viral infections (Gajdusek and Zigas, 1957; Torrey et al., 1982; Jones et al., 1985; Amsterdam et al., 1985; Crow, 1987). In addition, several psychotropic drugs appear to have anti-viral activity and can inhibit viral replication (Chang, 1975; Wunderlich et al., 1980; Bohn et al., 1983; Shaskan et al., 1985; Patou et al., 1986; Ziaie and Kefalides, 1989; Ziaie et al., 1994). For example, several in vitro studies have reported inhibition of Herpes simplex virus (Skinner et al., 1980; Buchan et al., 1988; Ziaie and Kefalides, 1989; Ziaie et al., 1994), while clinical studies have shown a reduced rate of Herpes simplex virus infections (Skinner, 1983; Amsterdam et al., 1990, 1991, 1996). In this regard, we observed a reduction

*Corresponding author. Present address: Univesity Science Ctr-8th floor, 3600 Market St., Philadelphia, PA 19104, USA. Tel.: +1 215 6623452; fax: +1 215 6626443.

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in the rate of oral-labial Herpes type-I infections (Amsterdam et al., 1990; Rybakowski and Amsterdam, 1991) and a reduction in the mean number, episode duration and symptom severity of genital Herpes type-II infections in healthy, non-psychiatric women (Amsterdam et al., 1991, 1996) during oral lithium therapy.

In this preliminary report, we examined the possibility that chronic psychotropic drug therapy may reduce the reported yearly recurrence rate of flu-like infections in patients taking chronic lithium or antidepressant medication.

2. Methods

2.1. Subjects

We queried 236 affective disorder patients regarding prior rates of yearly flu-like infections: 177 taking lithium carbonate and 59 taking antidepressants (tricyclics, monoamine oxidase inhibitors or fluoxetine) on a chronic basis. All subjects were treated in a naturalistic fashion at the affective disorders outpatient clinics of the Hospital of the University of Pennsylvania and Medical Academies of Poznan, Poland. All fulfilled Research Diagnostic Criteria (Spitzer et al., 1978) for past or present primary, endogenous, unipolar or bipolar affective disorder (Table 1). None of the patients was psychotic or demented, and all had received psychotropic medication for at least one year.

Given the naturalistic treatment setting, evaluations were performed while some patients were in the midst of an affective episode and others in remission. Several lithium subjects were also receiving concomitant, short-term antidepressant medication for a depressive episode, and some patients in both groups took concomitant sedative medication for insomnia. All of the subjects were in good physical health, and none had a history of significant hepato-renal, endocrinologic, hematologic or immunologic disease.

Table 1
Descriptive features of patients

	Lithium (n = 177)	Other antidepressants (n = 59)
Gender		
Men	68 (38%)	20 (34%)
Women	109 (62%)	39 (66%)
Age (mean ± S.D.)	46±13	46±13
Treatment duration (mos)	101±67	58±52
Average dose (mg/day) (mean ± S.D.)	1160±291	–
Average lithium level (mmol/l)	0.83±0.12	–

After providing informed consent, each subject was queried using a structured interview to retrospectively assess the presence or absence of several infectious diseases including flu-like illness. Patients were asked to provide their best estimate of the yearly average number of flu-like infections experienced prior to receiving their current psychotropic drug treatment.

They were then queried regarding the average number of flu-like infections in the preceding 2 years. Flu-like illness was defined as an upper respiratory infection with symptoms such as fever, malaise, body aches and rhinorrhes, lasting for 3 or more consecutive days. Responses were recorded on a standardized report form for pooled data analyses.

2.2. Statistical procedures

Flu-like infections before and during treatment were analyzed by calculating the mean within subject change in infection rates in the lithium and antidepressant groups, as well as analyzing the proportion of subjects with < 1 episode per year and with any reduction in the number of occurrences per year. Chi square analysis was used to test for differences in the proportions, and t test statistics were used to examine the significance of group differences in the mean change in yearly flu-like infection rates. Additionally, analysis of covariance (ANCOVA) for the mean during treatment was conducted with the pretreatment mean serving as the covariate factor. Analyses were repeated using nonparametric Wilcoxon sign rank tests for within-group effects over time and the Wilcoxon rank sum test for between-group differences.

We constructed a model comparing lithium vs. antidepressant group differences adjusted for the variables age, gender and duration of treatment. The test was constructed using a logistic regression

model with any reduction in flu-like infections as the dependent variable. This analysis was repeated for the mean change in flu-like infection rates using multiple linear regression. All tests were performed using the SAS statistical package, with significance levels estimated using two-tailed statistics and a significance level set at 0.05.

3. Results

The mean number of yearly flu-like episodes decreased significantly during lithium treatment ($P < 0.001$), while a more modest reduction was seen during chronic antidepressant therapy ($P < 0.10$) (Table 2). However, the change in mean infection rates between treatment groups was not statistically significant ($P =$ ns). An ANCOVA of the mean number of infections during treatment-adjusting for the pretreatment mean value-confirmed this result ($F = 1.41$, df = 2,228, $P = 0.24$).

50 of 234 subjects (21%) reported having < 1 pretreatment flu-like episodes per year: 43 of 176 (24%) on lithium and 7 of 58 (12%) on antidepressants ($X^2 = 3.97$; $P < 0.05$). During treatment, the proportions increased to 42% and 19% respectively ($X^2 = 10.1$; $P < 0.001$) (Table 2).

Overall, 32% of patients reported a reduction in flu-like episodes during treatment, while 62% had no change and 5% an increase. Of 173 lithium patients, 59 (34%) reported a reduction while 106 (61%) and 8 (5%) had no change or an increase, respectively. Similarly, 16 of 58 (28%) patients on antidepressants had a reduced infection rate, while 38 (65%) and 4 (7%) had no change or an increase, respectively ($X^2 = 0.84$; $P =$ ns).

Finally, age, gender and duration of treatment were not associated with a change in infection rates. However, a logistic regression analysis showed that (after controlling for the aforementioned variables) men (43%) were more likely to have a reduction in infection rate than women (28%) ($P < 0.05$).

4. Discussion

Although preliminary in nature and based upon retrospective reports, our observation of a reduced infections rate during chronic psychotropic drug treatment complements earlier in vitro reports of anti-viral activity with psychotropic drugs. In this

Table 2
Mean frequency and proportion of flu-like episodes per year

	Pretreatment	During treatment	Difference	*t*-test *P* value	Wilcoxon *P* value
Mean ± S.D.					
Lithium	1.48±1.13	1.14±1.20	0.34±0.92	0.001	0.001
Other	2.15±2.19	1.76±1.86	0.39±1.69	0.08	0.02
t-test					
t	2.21	2.36	0.24		
df	67.5	75.4	68.7		
P value	0.03	0.004	0.81		
Wilcoxon					
P value	0.02	0.004	0.47		
Proportion with < 1 flu-like episode/yr					
Lithium	24%	42%			
Other	12%	19%			
χ^2	3.97	10.11			
P value	0.05	0.001			
Proportion with a reduction in episodes					
Lithium			34%		
Other			28%		
χ^2			0.84		
P value			0.36		

regard, anti-viral activity has been demonstrated with sulpiride (Patou et al., 1986), trifluoperazine (Patou et al., 1986), chlorpromazine (Chang, 1975; Krizanova et al., 1982; Bohn et al., 1983; Patou et al., 1986), haloperidol (Wunderlich et al., 1980) and lithium (Skinner et al., 1980; Hartley, 1983; Buchan et al., 1988). There is also evidence from case reports (Lieb, 1979, 1981; Gilis, 1983) and clinical studies of anti-viral activity with lithium carbonate and several antidepressants. For example, Skinner (1983) reported a reduction in symptom severity and viral excretion in 73 healthy women with genital Herpes infections treated with lithium succinate ointment (vs. placebo). More recently, we reported a reduction in the recurrence rate of oral-labial Herpes infections during chronic treatment with lithium and antidepressants in affective disorder patients (Amsterdam et al., 1990; Rybakowski and Amsterdam, 1991). In subsequent prospective, double-blind, placebo-controlled trials we observed a reduction in the recurrence rate and severity of recurrent genital Herpes infections during oral lithium treatment in healthy, non-psychiatric women (Amsterdam et al., 1991, 1996).

Several mechanisms have been proposed to explain the antiviral action of psychotropic drugs. These include replacing magnesium ion with lithium as an enzyme cofactor in viral protein synthesis (Bach and Specter, 1988), inhibition of viral DNA polymerase (Skinner et al., 1980), altered lymphocyte and macrophage function (Friedenberg and Marx, 1980), reduced T-suppressor lymphocyte activity (Shenkman et al., 1978; Lieb, 1981), altered prostaglandin E_1 and free fatty acid synthesis (Horrobin, 1985; Horrobin et al., 1988) and altered host cell membrane dynamics reducing viral penetration of the cell (Bohn et al., 1983; Gosztonyi and Ludwig, 1984; Shaskan et al., 1985). More recently, Ziaie and Kefalides (1989) found that lithium ion had a cyto-protective action and restored host-cell protein synthesis while reducing viral protein synthesis in Herpes-infected cells. Subsequently, these investigators reported that lithium also inhibited Herpes virus replication in a dose-dependent fashion with mRNA for host-cell protein maintained while mRNAs for viral protein and DNA polymerase was almost absent (Ziaie et al., 1994).

Several caveats should be considered in the interpretation of the present data. For example, there are obvious limitations to the use of retrospective, patient-reported data, and its validity might well be questioned. In this regard, the patients were in treatment for an average of 5–8 years and were asked to report the presence of flu-like illness which occurred years earlier. Moreover, factors such as recall bias, whereby patients may misremember or misdate the occurrence of flu-like illness might account for the present findings. Similarly, some patients might confuse the symptoms of prior flu-like illness with those of recurrent affective illness during which they experienced symptoms of fatigue, malaise and muscle aches. Clearly, a prospective study documenting the frequency of flu-like infections would have been much more desirable.

Clinical factors other than a direct anti-viral action of psychotropic drugs could also account for our observation. For example, a reduction in stress-induced viral reactivation (Landmann et al., 1984; Glaser et al., 1985; Schleifer et al., 1985) or mood stabilization with psychotropic drugs might enhance immunologic status and diminish the number of viral infections (Fernandez and Fox, 1980; Sengar et al., 1982; Kiecolt-Glaser et al., 1985). Obviously, direct measurement of immune-competence in our subjects would have been desirable, and should be pursued in future prospective studies. Finally, we did not assess the rate of flu-like episodes in a non-psychiatric control group. The inclusion of such a group might have altered the interpretation of the present results.

In conclusion, in this preliminary report we observed a small but significant reduction in the mean rate of flu-like episodes during lithium treatment ($P < 0.001$), and a more modest reduction during chronic treatment with antidepressants ($P < 0.10$). This reduction was the greatest in men taking lithium ($P < .05$). These preliminary observations support the possibility that some psychotropic drugs have anti-viral activity.

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References

Amsterdam, J.D., Winokur, A., Dyson, W.L., Herzog, S., Gonzalez, F., Rott, R. et al., 1985. Borna disease virus: a possible etiologic factor in human affective disorders. Arch. Gen. Psychiatry 42, 1093–1096.

Amsterdam, J.D., Maislin, G., Rybakowski, J., 1990. Possible anti-viral action of lithium carbonate in herpes simplex virus infections. Biol. Psychiatry 27, 447–453.

Amsterdam, J.D., Maislin, G., Potter, L., Giuntoli, R., Koprowski, H., 1991. Suppression of recurrent genital herpes infections with lithium carbonate: A randomized, placebo-controlled study. Lithium 2, 17–25.

Amsterdam, J.D., Maislin, G., Hooper, M.B., 1996. Suppression of herpes simplex virus infection with oral lithium carbonate – a possible antiviral activity. Pharmacotherapy 16, 1070–1075.

Bach, R.O., Specter, S., 1988. Antiviral activity of the lithium ion with adjuvant agents. In: Birch, N.J. (Ed.), Lithium: Inorganic Pharmacology and Psychiatric Use. IRL Press, Oxford, pp. 91–92.

Bohn, W., Rutter, G., Hohenberg, H., Mannweller, K., 1983. Inhibition of measles virus budding by phenothiazines. Virology 130, 44–55.

Buchan, A., Randall, S., Hartley, C.E., Skinner, G.R.B, Fuller, A., 1988. Effect of lithium salts on the replication of viruses and non-viral microorganisms. In: Birch, N.J. (Ed.), Lithium: Inorganic Pharmacology and Psychiatric Use. IRL Press, Oxford, pp. 83–92.

Chang, T.-W., 1975. Suppression of herpetic recurrence by chlorpromazine. New Engl. J. Med. 293, 153–154.

Crow, T.J., 1987. Genes and viruses in schizophrenia: The retrovirus/transposition hypothesis. In: Kurstak, E., Lipowski, Z.J., Morozov, P.V. (Eds.), Viruses, Immunity, and Mental Disorders. Plenum, New York, pp. 125–134.

Fernandez, L.A., Fox, R.A., 1980. Perturbation of the human immune system by lithium. Clin. Exp. Immunol. 41, 527–532.

Friedenberg, W.R., Marx, J.J., 1980. The effect of lithium carbonate on lymphocyte, granulocyte, and platelet function. Cancer 45, 91–97.

Gajdusek, D.C., Zigas, V., 1957. Degenerative disease of the central nervous system in New Guinea. New Engl. J. Med. 257, 974–978.

Gilis, A., 1983. Lithium in herpes simplex. Lancet ii, 1209–1210.

Glaser, R., Kiecolt-Glaser, J.K., Speicher, C.E., Holliday, J.E., 1985. Stress, loneliness, and changes in herpesvirus latency. J. Behav. Med. 8, 249–260.

Gosztonyi, G., Ludwig, H., 1984. Neurotransmitter receptors and viral neurotropism. Neuropsychiatr. Clin. 3, 107–114.

Hartley, C.E., 1983. The effect of lithium on Herpes simplex virus replication. Med. Lab. Sci. 40, 406.

Horrobin, D.F., 1985. Lithium in the control of herpesvirus infections. In: Bach, R.O. (Ed.), Lithium: Current Applications in Science, Medicine, and Technology. John Wiley, New York, pp. 397–406.

Horrobin, D.F., Jenkins, D.K., Mitchell, J., Manku, M.S., 1988. Lithium effects on essential fatty acid and prostaglandin metabolism. In: Birch, N.J. (Ed.), Lithium: Inorganic Pharmacology and Psychiatric Use. IRL Press, Oxford, pp. 173–176.

Jones, J.F., Ray, C.G., Minnich, L.L., Hicks, M.J., Kibler, R., Lucas, D.O., 1985. Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies. Ann. Intern. Med. 102, 1–7.

Kiecolt-Glaser, J.K., Stephens, R.E., Lipetz, P.D., Speicher, C.E., Glaser, R., 1985. Distress and DNA repair in human lymphocytes. J. Behav. Med. 8, 311–320.

Krizanova, O., Ciampor, F., Veber, P., 1982. Influence of chlorpromazine on replication of influenza virus in chick embryo cells. Acta Virol. (Praha) 26, 209–216.

Landmann, R.M.A., Muller, F.B., Perini, C.H., Wesp, M., Erne, P., Buhler, F.R., 1984. Changes in immunoregulatory cells induced by psychological and physical stress: relationship to plasma catecholamines. Clin. Exp. Immunol. 58, 127–135.

Lieb, J., 1979. Remission of recurrent herpes infection during therapy with lithium. New Engl. J. Med. 301, 942.

Lieb, J., 1981. Remission of herpes virus infection and immunopotentiation with lithium carbonate: inhibition of prostaglandin E1 synthesis by lithium may explain its, antiviral, immunopotentiating, and antimanic properties. Biol. Psychiatry 16, 695–698.

Patou, G., Crow, T.J., Taylor, G.R., 1986. The effects of psychotropic drugs on synthesis of DNA and the infectivity of Herpes simplex virus. Biol. Psychiatry 21, 1221–1225.

Rybakowski, J., Amsterdam, J.D., 1991. Lithium prophylaxis and recurrent labial herpes infections. Lithium 2, 43–47.

Schleifer, S.J., Keller, S.E., Siris, S.G., Davis, K.L., 1985. Depression and immunity. Lymphocyte function in ambulatory depressed patients, hospitalized schizophrenic patients, and patients hospitalized for herniorrhaphy. Arch. Gen. Psychiatry 42, 129–133.

Sengar, D.P.S., Waters, B.G.H., Dunne, J.V., Bouer, I.M., 1982. Lymphocyte subpopulations and mitogenic responses of lymphocytes in manic-depressive disorders. Biol. Psychiatry 17, 1017–1022.

Shaskan, E.G., Oreland, L., Wadella, G., 1985. Dopamine receptors and monoamine oxidase as virion receptors. Perspect. Biol. Med. 27, 239–250.

Shenkman, L., Borkowsky, W., Holzman, R.S., Shopsin, B., 1978. Enhancement of lymphocyte and macrophage function in vitro by lithium chloride. Clin. Immunol. Immunopathol. 10, 187–192.

Skinner, G.R.B., Hartley, C., Buchan, A., Harper, L., Gallimore, P., 1980. The effects of lithium chloride on the replication of Herpes simplex virus. Med. Microbiol. Immunol. 168, 139–148.

Skinner, G.R.B., 1983. Lithium ointment for genital herpes. Lancet ii, 288.

Spitzer, R.L., Endicott, J., Robins, E., 1978. Research diagnostic

criteria: rationale and reliability. Arch. Gen. Psychiatry 35, 773–782.

Torrey, E.F., Tolken, R.H., Winfrey, C.J., 1982. Cytomegalo-virus antibody in cerebrospinal fluid of schizophrenic patients detected by enzyme immunoassay. Science 216, 892–894.

Wunderlich, V., Fey, F., Sydow, V.S., 1980. Antiviral effect of haloperidol on Rauscher murine leukemia virus. Arch. Geschwulstforsch 50, 758–762.

Ziaie, Z., Kefalides, N.A., 1989. Lithium chloride restores host protein synthesis in herpes simplex virus infected endothelial cells. Biochem. Biophys. Res. Comm. 160, 1073–1078.

Ziaie, Z., Brinker, J.M., Kefalides, N.A., 1994. Lithium chloride suppressed the synthesis of messenger RNA for infected cell protein-4 and viral deoxyribonucleic acid polymerase in herpes simplex virus infected endothelial cells. Lab. Invest. 70, 29–38.